Hypothesis

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Abstract: Forensic institutions throughout the country house patients with severe psychiatric illness and history of criminal violations. Improved medical care, hygiene, and nutrition led to unmatched longevity in this population which previously lived on average 15 to 20 years shorter than the public at large. On the other hand, longevity has contributed to increased prevalence of age-related diseases, including neurodegenerative disorders, which complicate clinical management. Forensic institutions, originally intended for the treatment of younger individuals, are ill-equipped for the growing number of older offenders. Moreover, as antipsychotic drugs became available in 1950s and 1960s, we are observing the first generation of forensic detainees who had aged on dopamine blockers. Although the consequences of long-term treatment with these agents are unclear, schizophrenia-associated gray matter loss, may contribute to the development of early dementia. Taken together, increased lifespan and subsequent cognitive deficit observed in long-term psychiatric institutions brought forth questions and dilemmas unencountered by the previous generations of clinicians, such as: 1. Does the presence of neurocognitive dysfunction justify antipsychotic dose reduction or discontinuation despite a lifelong history of schizophrenia and violent behavior? 2. Should neurolipidomic interventions become the standard of care in elderly individuals with lifelong schizophrenia and dementia? 3. Can patients with schizophrenia and dementia meet the Dusky standard and stand trial? 4. Should neurocognitive disorders in elderly with lifelong schizophrenia be treated differently than age-related neurodegeneration? In this article, we describe strategies for potentially slowing the development of neurocognitive disorders in forensic patients with chronic mental illness by adopting a three-prong strategy: 1. Approaching lifelong psychosis from microbial and immunological perspective. 2. Identify modifiable risk factors for age-related diseases in forensic institutions. 3. Utilizing novel receptor-independent treatments for chronic psychosis.

Keywords: neurodegenerative disorders; schizophremia; pdk1 inhibitors; lipid replacement therapy; aryl hydrocarbon receptor antagonists

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Long term psychiatric institutions remain in existence because the outcome of schizophrenia and schizophrenia-like disorders has been unsatisfactory. At present, criminal behavior cannot, without speculation, be accredited to specific brain areas or pathologies, but this may change in the future. Improved care has prolonged the life of patients with chronic psychosis and history of criminal behavior residing in state hospitals. Longevity in chronic psychiatric patients predisposes to the development of dementia, engendering a new pathology: neurodegeneration superimposed on chronic psychosis. Receptor-independent antipsychotic strategies revolve around gut barrier rehabilitation, averting microbial translocation, and restoring the homeostasis of neuronal membrane.

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Introduction

The population worldwide is aging at a rapid pace and so are forensic detainees with severe psychiatric illnesses, including schizophrenia (SCZ) and schizophrenia-like disorders (SLDs). In forensic institutions, there are two subpopulations of elderly patients with neurocognitive disorders: career criminals with lifelong mental illness and elderly first offenders without previous psychiatric history. The latter category includes patients with frontotemporal dementia behavioral variant (bvFTD), a condition with clinical manifestations similar to those of schizophrenia (SCZ). As the incidence of bvFTD has increased dramatically in forensic population over the past two decades, screening all first offenders after the age of 50 could identify this disorder early to ensure adequate adjudication and placement, while and at the same time, decongesting the crowded State hospitals.

At the cellular level, bvFTD has been associated with the selective loss of von Economo neurons (VENs), large cells, located in the anterior cingulate cortex (ACC), insular cortex (IC), and frontopolar cortex (FPC). As VENs belong to the human neuro-moral network which plays a key role in amiability and empathy, loss of these cells is believed to engender a type of acquired sociopathy (1)(2)(3). Interestingly, dysfunctional ACC, IC and FPC have been associated not only with SCZ but also with impaired disease awareness or anosognosia, a common SCZ characteristic which increases the odds of criminal violations (4)(5)(6)(7). Indeed, several recent studies have suggested that anosognosia may be a better predictor of criminal behavior than focal brain lesions or clinical diagnoses (8)(9)(10).

Improved medical care, sanitation, and nutrition have contributed to increased longevity in both the population at large and institutionalized individuals with criminal history and chronic SCZ or SLDs (11)(12)(13). On the other hand, increased lifespan has engendered a novel pathology, late-life dementia in people living with SCZ (PLWS), a complex entity difficult to manage in forensic institutions (14)(15). The complexity is further compounded by the long-term treatment with dopamine (DA) blocking drugs, agents associated with serious adverse effects in patients with dementia (18)(19). This begets a clinical dilemma, as treatment of chronic psychosis can harm patients with dementia, while nontreatment may contribute to the reemergence of violent behaviors. For this reason, new therapeutic strategies are urgently needed to address this conundrum, strategies which may involve neurolipidomic approaches, restoration of gut barrier homeostasis and other receptor-independent antipsychotic treatments (RIATs)(20)(21).

Exposure to typical and atypical antipsychotic drugs and chronic DA depletion was demonstrated to disrupt synaptic plasticity, contributing to impaired learning of new information (22)(23)(24). When superimposed on late-life dementia, dysfunctional neuroplasticity leads to more pronounced cognitive deficits, consistent with a distinct pathological entity (25)(26). Indeed, under physiological circumstances, healthy aging was associated with increased synthesis of striatal DA, probably to compensate for the age-related downregulation of DA receptors (27)(28)(29). Loss of synaptic plasticity, a modifiable risk factor, may be reversed via neurolipidomic therapies and/or DA reuptake inhibitors (DRIs), suggested by some researchers and clinicians (30).

Antipsychotic drugs exert receptor-dependent and receptor-independent pharmacological actions, the former have been well-defined and frequently referred to, while the latter are rarely mentioned in the literature. Receptor-independent properties of antipsychotic drugs, include antimicrobial, antiproliferative, pro-autophagy, anti-endocytic as well as lysosomotropism and peroxidation of plasma membrane lipids (31)(32)(33)(34)(35). Indeed, several first and second-generation antipsychotic drugs were demonstrated to disrupt neuronal and non-neuronal cells by oxidation of membrane lipid bilayer. This in return, distorts the cell surface, altering receptor signaling as well as the transcellular transport. At the level of intestinal epithelia, antipsychotic drugs-mediated peroxidation of lipids in plasma membranes, increases gut permeability, facilitating microbial translocation into host tissues (34)(36)(37)(38)(39)(40)(Figure 1).

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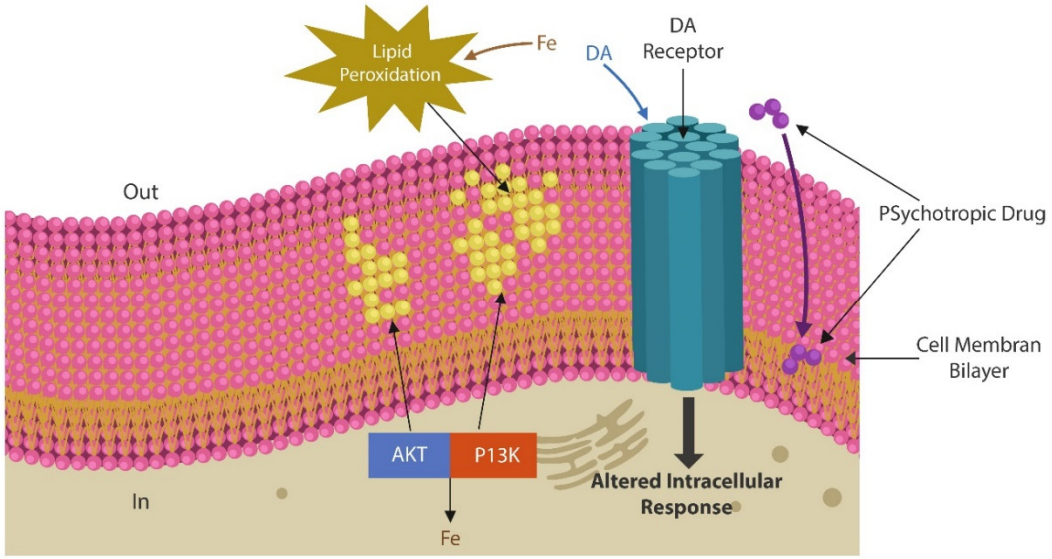

Figure 1. Neuronal membranes are comprised of a lipid bilayer which anchors numerous neurotransmitter receptors. Antipsychotic drugs and excessive iron trigger peroxidation of the lipid bilayer, altering membrane permeability. Intracellular iron activates the downstream SCZ-related phosphatase, including Akt and PI3K contributing to the pathogenesis of this disease. Psychotropic drugs, especially those belonging to the thiazine group, intercalate themselves into the lipid bilayer, changing the biophysical properties of plasma membranes which in turn, disrupts neurotransmission.

Another receptor-independent property of antipsychotic drugs is interference with iron metabolism (41)(42)(43). As DA functions as a "de facto" iron chelator, it averts lipid peroxidation by sequestrating iron; conversely antipsychotic drugs upregulate iron, predisposing to neuronal death by ferroptosis (44)(45). Indeed, induced ferroptosis, a new form of chemotherapy, has been utilized for eliminating neuroblastoma, a malignancy sensitive to iron overload (46)(47). Along this line, antipsychotic drugs-induced gray matter loss, reported by several neuroimaging studies, may be taking place by ferroptosis (48)(49)(50).

In this article, we discuss RIATs, including lipid replacement therapy (LRT), recombinant human IL-22, and aryl hydrocarbon receptor (AhR) antagonists. We also take a closer look at the dysfunctional interoceptive awareness and its role in bvFTD and recommend screening older first offenders for this disorder to identify it early and ensure proper sentencing and placement.

The neuroscience of criminal behavior

For the past two centuries, the relationship between neuroscience and criminal law has been an uneasy one. Due to the complexity of criminal behavior and overlapping brain areas driving behavioral responses, a crime cannot, without speculation, be directly corelated to a specific central nervous system (CNS) region or pathology, a situation which may change as the molecular underpinnings of cellular cognition are better defined (51). In addition, the disappointing results of schizophrenia (SCZ) outcome studies and the continued need for public institution to treat chronic mentally ill patients comprise proof of concept that a direct link between brain pathology and specific behaviors remains elusive (52)(53)(54). For example, the well-known actor, Robin Williams who died by suicide, had Lewy body disease (LBD), however, linking this pathology to suicide would not be accepted in a court of law as most people with this disease do not take their lives (55). Another example, Charles Whitman, an individual who committed mass murder in 1966, had a brain tumor

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involving amygdala, however, the extent to which this pathology contributed to his crime, if any, cannot be ascertained as individuals with similar conditions may not engage in violent acts (56).

Interoceptive awareness is the ability to perceive internal state of the body, such as the heart rate, respiration, position and belonging of limbs, in other words, human self-awareness or insight are dependent on this system. Interoceptive awareness can be impaired in various pathologies, including strokes of the right hemisphere. For example, stroke-related neurological deficits can give patients the false impression that the left limbs do not belong to them, linking left-sided neglect to the faulty right hemisphere (57)(58).

Like stroke, SCZ, bvFTD, and chronic traumatic encephalopathy (CTE) can be associated with anosognosia and neglect of body functions as specific brain areas may misprocess information, giving patients false impression or illusions which lead to erroneous beliefs known as delusions, suggesting that anosognosia begets psychosis, rather than the other way around (59)(60)(61). Since VENs have been associated with interoceptive awareness and a larger number of VENs reside in the right hemisphere compared to the left, it is reasonable to suggest that anosognosia is a function of the right IC, ACC, and FPC. As poor illness insight is found in up to 98% patients with SCZ, this disorder likely originates in the right hemisphere and probably disinhibits the speech areas in the left brain, accounting for auditory hallucinations (62). In addition, SCZ was associated with decreased number of VENs, cells of growing significance in this disorder, consistent with the idea that anosognosia leads to psychosis (63)(64)(65). Moreover, as anosognosia is a cognitive symptom, SCZ may be primarily a cognitive disorder in which psychosis is a secondary phenomenon, an observation endorsed by Emil Kraepelin (66).

Anosognosia became the focus of research during the COVID-19 pandemic which, like HIV, could lead to poor insight into cognitive impairment (67)(68)(69)(70). Discovered in 1925 by Constantin von Economo, VENs are unique, elongated, spindle shaped cells, documented in advanced mammals, which are present in higher number in humans compared to any other animal. In addition, VENs emerge after birth and their number increases gradually until the age of four, coinciding with the preoperational stage of development when children become capable of symbolical thinking, further linking VENs to insight (69(71)(72)(73) Interestingly, the number of VENs does not decrease during healthy aging, showing that loss of these cells may contribute to dementia (73). Furthermore, VENs comprise the brain salience network (SN), a cortical neuronal hub associated with interoceptive awareness and insight which under pathological conditions, may lead to SCZ, bvFTD, and violent behavior (69)(74).

Schizophrenia as a segmental progeria

Segmental progeria, as SCZ is often called by researchers, is a syndrome of accelerated cellular aging marked by shortened telomeres which drive both neurodegeneration and all-cause mortality (75)(76). As a result, PLWS have an average lifespan of 15-20 years shorter compared to their healthy counterparts. However, due to improved care over the past three decades, the lifespan of this population has increased considerably, predisposing to neurodegenerative pathology (77)(78).

Cellular senescence is an anticancer program of proliferation arrest, resistance to apoptosis, and active metabolism marked by a proinflammatory secretome, named senescence-associated secretory phenotype (SASP) which can spread senescence to the neighboring healthy cells in a paracrine fashion (79)(80). Senescence may explain the low-grade inflammation which plays a major role in SCZ onset and maintenance. Indeed, SCZ-associated premature cellular senescence affects all tissues and organs, including the gut and blood-brain barrier (BBB), likely accounting for increased microbial translocation from the gastrointestinal (GI) tract into the host systemic circulation (81). In this regard, lipopolysaccharide (LPS), a cell wall component of Gram-negative bacteria, was detected postmortem in Alzheimer's disease (AD) brains, suggesting that it migrates from the gut through a senescent intestinal barrier (82). This is significant as impaired intestinal permeability was documented in SCZ, explaining the high comorbidity of this disorder with inflammatory bowel disease (IBD)(81)(83).

Upon CNS entry, microbes, or their components, including LPS or mcfDNA, activate microglia, converting these brain macrophages into neurotoxic cells known to engage in the elimination of

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healthy neurons, probably including VENs (84). Furthermore, a recent study detected plasma antibodies against specific gut microbes, including *Hafnei alvei, Pseudomonas aeruginosa, Morganella morganii, Pseudomonas putida, and Klebsiella pneumoniae* in patients with negative SCZ symptoms, linking this condition to microbial translocation (85)(86).

Treatment with antipsychotic drugs affect neuronal cells via receptor-dependent and receptor-independent mechanisms. The latter include, among other changes, peroxidation of cell membrane lipids and intercalation of the drug in neuronal membrane's lipid bilayer (37)(87)(88)(89)(Figure1). Moreover, antipsychotics-induced peroxidation of cell membrane lipids and iron upregulation may trigger neuronal loss by ferroptosis, a nonapoptotic cell death caused by excessive iron in the context of decreased antioxidants, such as glutathione peroxidase 4 (GPX-4)(90)(91).

We hypothesize that, due to their large size, VENs are vulnerable to lipid peroxidation, explaining the preferential loss of these cells in bvFTD and probably SCZ (92). Moreover, mcfDNA, derived from the disintegration of translocated bacteria, induces Tau hyperphosphorylation and its accumulation in VENs, leading to the selective demise of these cells (3)(93). This may be significant as anti-ferroptotic agents as well as iron chelators may comprise viable treatment options for bvFTD and other dementias (94)(95)(96).

Schizophrenia outcome studies - Kraepelin was right!

Numerous studies have shown unfavorable longitudinal progress in SCZ, accounting for the continued need for long-term psychiatric facilities, such as State hospitals. For example, a century ago, there were large public institutions for tuberculosis, leprosy, and mental illness, while today only the latter remain in existence (52). This is proof of concept that sustained recovery in patients with SCZ or SLDs remains inadequate. Indeed, those of us who work routinely with SCZ patients, know that only a small number of individuals diagnosed with this disorder return to their premorbid level of functioning (97)(98)(99). For example, 33% of SCZ patients relapse during the first 12 months after an initial psychotic episode, 26% remain homeless at 2 years follow-up, while 5 years after the first psychotic outbreak, only 10% are employed (100)(101)(102). Overall, 13.5% of SCZ patients meet recovery criteria at any point in time after the first psychotic episode (102). These outcome studies are in line with a large metanalysis by Warner, R who looked at the entire 20th century and found that prognosis today is not different than in the first decades of the past century (103)(53) (Table 1).

Table 1. Sustained recovery of SCZ patients during the 20th century, Including employment (Table adapted from Warner R data).

INTERVAL	SUSTAINED RECOVERY	EMPLOYED
1901- 1920	20%	4.7%
1921- 1940	12%	11.9%
1941- 1955	23%	4.1%
1956- 1975	20%	5.1%
1976- 1995	20%	6.9%

Furthermore, contrary to the expectations of most clinicians, the recovery rate following the introduction of antipsychotic drugs was not very different compared to the pre-psychopharmacological era (53). Moreover, other studies have shown that employment of SCZ patients has decreased steadily over the past decades, a finding in line with neuroimaging studies which show lifelong gray matter loss, causing progressive disability (72)(104) (Figure 2).

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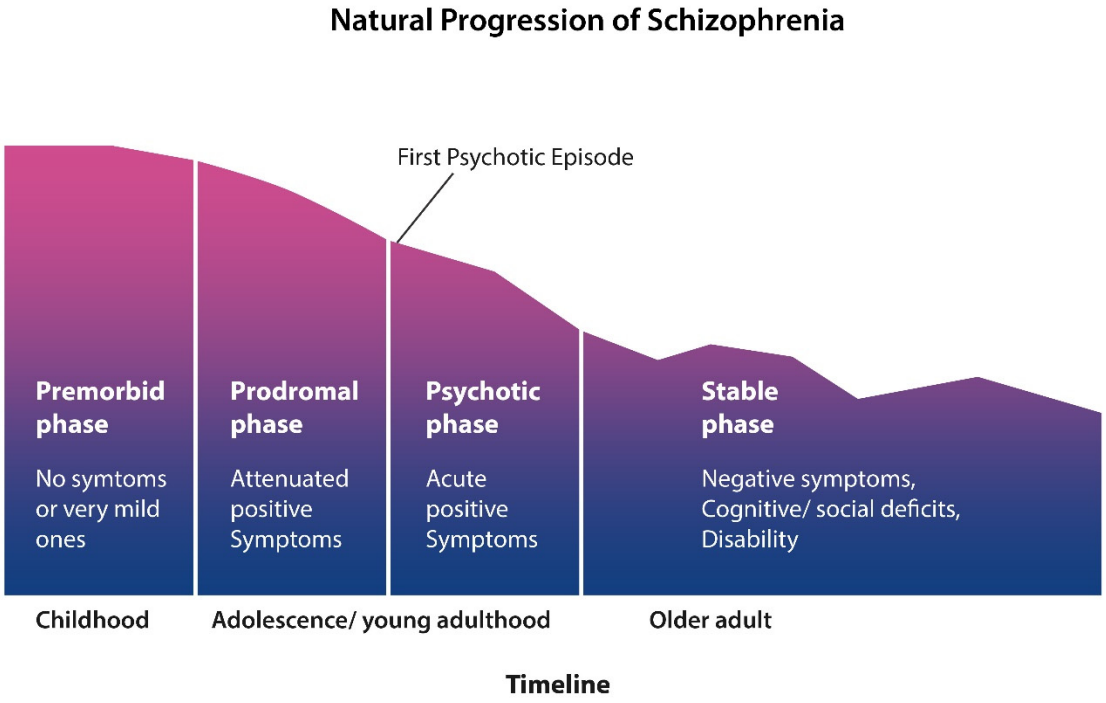

Figure 2. Natural course of SCZ starts in early childhood with a premorbid phase with no symptoms or very mild signs. Prodromal phase is marked by mild symptoms, such as social isolation, anxiety, and insomnia. This phase blends gradually into the psychotic phase during which patients are usually hospitalized numerous times for exhibiting positive symptoms. Around midlife the positive symptoms gradually subside and are replaced by disabling negative, and cognitive manifestations. (Table adapted from ref. 105).

Indeed, progressive cortical tinning which seems to occur regardless of antipsychotic treatment is in line with the natural progression of SCZ toward disability and cognitive deterioration (106)(107)(108)(Figure 2). In contrast to AD which is characterized by impaired recall, cognitive problems in schizophrenia stem primarily from dysfunctional learning of new information (15)(109). We surmise that defective VENs and the subsequent anosognosia are drivers of SCZ, while all the other symptoms may be secondary to this pathology.

Taken together, SCZ outcome studies suggest that the long-term evolution of chronic psychotic disorders leads to disability and cognitive deficits, regardless of treatment with DA-blocking agents. Moreover, anosognosia, the cardinal and driving SCZ mechanism, is rarely ameliorated by DA-blockers, suggesting that these drugs do not affect the root cause of the disease. Furthermore, novel data has corelated anosognosia with aggressive behaviors.

The molecular basis of SCZ and dementia: Tau protein loss of function

SCZ and dementia likely meet at the molecular level as both conditions have been associated with microtubular instability. Recent studies have demonstrated that SCZ is characterized by decreased microtubule-associated protein 2 (MAP2) or Tau which functions as a "molecular velcro", holding axonal microtubules (MTs) together (110)(Figure 3).

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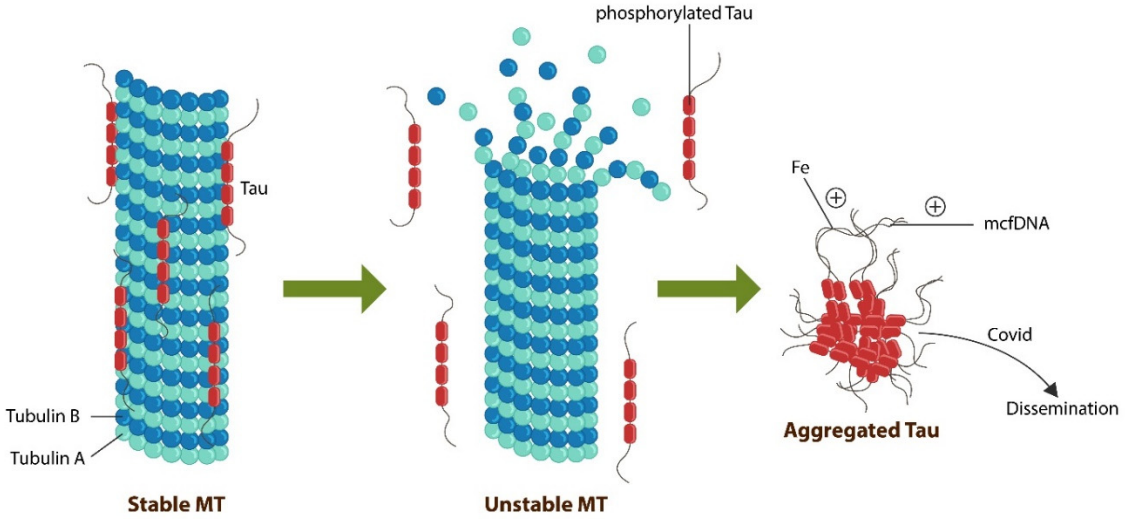

Figure 3. MTs are stabilized by MAP2 or Tau protein. Excessive Tau phosphorylation detaches this protein, destabilizing the MTs. Hyperphosphorylated Tau can aggregate, forming neurofibrillary tangles (NFTs), which accumulate, triggering neuronal death. Both iron and mcfDNA promote Tau aggregation, while pathogens, including COVID disseminate pathological Tau to neighboring healthy cells, facilitating the pathogenesis of dementia.

MTs are components of cellular cytoskeleton which, aside from maintaining the cell shape, participate in awareness and insight, suggesting that at the molecular level, anosognosia in SCZ may be the result of unstable MT due to decreased Tau (111)(112)(113). Indeed, anosognosia in SCZ may be caused by dysfunctional MTs in VENs, cells with long axons which rely on MTs for intracellular communication. Along this line, the role of MTs in cognition, self-awareness and insight is further substantiated by anesthesia as anesthetics bind MTs at the Tau site, likely destabilizing these proteins. Removal of Tau, may account for both loss of awareness during anesthesia and postoperative cognitive dysfunction (PCD)(114)(115). Another example of Tau-mediated insight impairment, is "chemo-brain", a phenomenon resulting from treatment of cancer patients with MT-targeting drugs, such as Taxol, which is often followed by changes in the cognitive and thought-process which may lower insight, linking further MTs to cognition and interoceptive awareness (116). Moreover, Tau and MTs are expressed in other tissues, including the heart which is known for possessing its own particular cognizance, distinct from the cortical awareness and memory (117)(118). For example, it has been established that following heart transplants, recipients often acquire not only select memories but also personality traits of the donor, further linking MTs to awareness, insight, and recall (119)(120)(121)(122). Indeed, local or cellular memory has been described in other tissues, including fascia, muscle, and gut microbiota, linking higher intellectual functions to MTs and Tau (123)(124). Furthermore, gut microbes contain primitive MTs and can transfer learned behavior from one cell to another, indicating that even rudimentary recall may be mediated by the MT and exported along with these molecules to other cells (125). Along this line, translocated microbes may 'instruct" host cells in Tau aggregation as microbial DNA promotes pathological Tau (126). Viruses, including SARS-CoV-2 can spread Tau aggregates or neurofibrillary tangles (NFTs) from cell to cell in a prion-like manner, indicating that microorganisms may alter cognition, insight, and interoception (127)(Figure 3). Furthermore, upregulated intracellular iron in senescent cells can also promote Tau aggregation, predisposing to neurodegeneration as well as to loss of VENs by ferroptosis.

As opposed to dementia, including bvFTD, SCZ lacks NFTs, however, loss of Tau protein and its function can engender same results, unstable MTs in VENs, altering information processing (113)(126)(129). Another VENs vulnerability that may lead to their preferential loss in bvFTD and possibly

SCZ, are lysosomes which appear to exhibit high affinity for NFTs, preferentially storing these aggregates (130).

Taken together, MTs have been hypothesized to play a major role in self-awareness, memory, and insight as they connect via integrins to extracellular matrix proteins, probably engendering CNS-wide molecular networks (131).

bvFTD: from insight to acquired psychopathy

BvFTD is a common, early-onset dementia and like other neurocognitive disorders is a clinical syndrome which can be easily confused with the primary psychiatric disorders, an error which in forensic setting can complicate patients' legal status, placement, and sentencing (132)(133). The clinical characteristics of bvFTD include, early onset (compared to AD), criminal behavior (reported in 37–57% of patients), and neuropsychiatric symptoms, including apathy, disinhibition, and compulsions (134)(135). An interesting and at the same time confusing features of bvFTD consist of criminal violations without overt memory loss, at least during the early disease phases, a puzzling situation for forensic evaluators who may not suspect a neurodegenerative disorder (136).

Lack of specific neuroimaging and laboratory biomarkers, especially in the early disease stages, adds to the challenges of differentiating this syndrome from SCZ, bipolar disorder, or major depressive disorder (MDD) (137). Indeed, over half of bvFTD patients had psychiatric diagnoses prior to the emergence of clear neurodegenerative signs, an error interfering with adequate management and court proceedings (138).

The prevalence of bvFTD in forensic setting has increased dramatically over the past decade (measured by the surge of late-life first offenders), highlighting the importance of educating the clinicians in keeping a high level of suspicion in first offenders over the age of 50. It is also crucial for the State hospitals to capture data on the number of older first offenders.

The correct diagnosis in forensic setting has a significant bearing on the adjudication and sentencing as judicial approach to criminal violations in individuals with neurodegenerative disorders is usually different than the classical "insanity defense" (139).

We recommend that all first offenders 50 years of age or older be screened for bvFTD. Screening should be accomplished by neuropsychological profile which usually reveal executive impairments and relative sparing of memory and visuospatial functions. Microbial translocation component can be evaluated by mcfDNA Karius Test®® and IL-22 Singulex-Erenna®® (Table 2). In addition, a task force should be established at local or state level, comprised of neuropsychologists, psychiatrists, and medicine/neurology to screen for bvFTD and report to courts for appropriate action. Along this line, in 2015 at Patton State Hospital, California, we have initiated a program for educating our clinicians on bvFTD via presentations, case reports, grand rounds, and publications to help identify this pathology early, if possible, at admission (140). This idea was later adopted by other groups and clinician education in bvFTD continues to be implemented up to date in various institutions and jurisdictions (139).
(https://www.reuters.com/article/us-crime-dementia/breaking-the-law-may-be-a-sign-of-dementia-idUSKBN0KE1Q020150105).

Like bvFTD, SCZ is a syndrome which in the second half of life is characterized by a "stable phase" with negative and cognitive symptoms, resembling dementia (Figure 2). This complicates not only the differential diagnosis but also the psychopharmacological management of SCZ with overlapping dementia. Indeed, comorbidity of SCZ with bvFTD or other dementias poses special challenges to the clinician as antipsychotic drugs were associated with serious, even fatal, adverse effects when administered to dementia patients (141)(142). In this regard, clinicians may find themselves in a catch 22 as continuing antipsychotic treatment in PLWS and comorbid dementia may risk untoward effects, while discontinuing this therapy may lead to the reemergence of the dangerous behaviors. This dilemma calls for an interdisciplinary approach and involvement of hospital bioethics committee.

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Neuropathological basis of bvFTD

VENs, numbering about 193,000 cells, are large, corkscrew neurons located in layer V of the IC, ACC, and FPC. These large, non-telencephalic cells project to various brain areas and participate in prosocial cognition, empathy, and emotional intelligence. As parts of the SN, VENs respond to endogenous or exogenous stimuli in the order of priority (69)(133).

SN dysfunction, documented in psychopathy and criminal behavior, connect this neuronal assembly to delinquency, however, depending on the jurisdiction, this evidence may not be allowed in a court of law (134). Interestingly, a recent study connected the SN with gut microbes *Prevotella* and *Bifidobacterium*, emphasizing that the microbiome can influence the function of VENs as well as the behavior, probably via MTs (144)(145). In addition, both *Prevotella* and VENs have been associated with suicidal behavior, further linking violence to dysfunctional gut permeability and microbial translocation outside the GI tract (146).

The homeostasis of intestinal barrier is maintained by interleukin 22 (IL-22), a cytokine regulated by aryl hydrocarbon receptor (AhR), a gut barrier protein responding to exogenous and endogenous ligands (63). In this regard, VENs-rich IC was demonstrated to keep the record of gut inflammations, emphasizing the tight link between the GI tract and insula (147)(148).

Dementia in PLWS, potential biomarkers

A novel marker of microbial translocation, mcfDNA, is likely to become a diagnostic tool for evaluating dementia in PLWS, while at the same time providing proof of concept that microbes can drive neuropathology (126)(149)(150). For example, the commercially available assay, mcfDNA Karius Test®® detects peripheral blood microbial DNA, a molecule demonstrated to drive Tau aggregation, predisposing to dementia (93)(126)(Table 2). Conversely, SCZ is characterized by downregulated Tau, indicating that this laboratory value could differentiate between SCZ with or without dementia (151)(152)(153)(154). For example, blood levels of phosphorylated tau (pTau) 217 and 181, elevated in dementia but normal in SCZ, can be helpful for differential diagnosis.

Another assay for gut barrier integrity available on the market, IL-22 Singulex-Erenna®®, measures IL-22 levels, a cytokine inversely corelated with gut barrier permeability and microbial translocation (Table 2). For example, low IL-22 with normal mcfDNA would reflect increased risk of microbial translocation without overt pathology. Conversely, low IL-22 and elevated mcfDNA would characterize frank bacterial translocation, requiring treatment. Interestingly, most antipsychotic drugs exert antibiotic properties, suggesting that blocking postsynaptic DA signaling may not be the only action mechanism of these agents. Moreover, IL-22 and mcfDNA could be useful for predicting the risk of relapse following discontinuation of antipsychotic drugs in forensic detainees.

Table 2. Standardized tests for dysfunctional gut barrier and translocation.

Marker Type	Marker Assay	References
Integrity of gut barrier	IL-22 Singulex-Erenna®®	155
Translocated microbes	mcfDNA Karius Test®®	156

Another marker that could differentiate SCZ from dementia, is ferritin (elevated in dementia and low in SCZ), implicating iron dysmetabolism in both syndromes (90)(157). Excessive intracellular iron associated with senescent cells, a predominant SCZ phenotype, was shown to induce Tau aggregation, implicating this biometal in tauopathies, including bvFTD (158)(159). Indeed, quantitative assessment of iron deposition is a new neuroimaging biomarker of bvFTD that can differentiate this phenotype from other FTD subtypes (160)(161). This suggests that in bvFTD, VENs may be lost through ferroptosis, a nonapoptotic cell death caused by iron-induced lipid peroxidation in the absence of glutathione-associated antioxidants. This is significant as intranasal deferoxamine was found effective for several neurodegenerative disorders, including bvFTD (162).

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Chronic Traumatic Encephalopathy

A condition similar to bvFTD, chronic traumatic encephalopathy (CTE), is a pathology associated with repeated traumatic brain injuries (TBIs), manifested by behavioral changes, including irritability, apathy, memory loss, and intermittent disorientation (163)(164)(165). Upregulated iron and pTau may be the common denominators of bvFTD and CTE, emphasizing that neurodegeneration can be initiated by a localized or more generalized and diffuse pathology (166)(167). Along this line, the former NFL player, Phillip Adams, who killed six people, and committed suicide while serving his sentence was found at autopsy to have had CTE, a condition some clinicians believed should have been factored in sentencing.

Interventions: receptor-independent antipsychotic treatments (RIATs)

The currently available antipsychotic drugs are extremely effective for the treatment of acute psychotic disorders, however their efficacy in chronic psychosis is much less dramatic and may even predispose to neurocognitive disorders by the lipid peroxidation of cell membranes. Dysfunctional cell membranes may lead to increased permeability of gut barrier and BBB, enabling microbial translocation from the GI tract into the systemic circulation, eventually reaching the brain.

Neurolipidomics is a rapidly growing field made possible by the recent advances in mass spectrometry (MS), a technique capable of quickly processing biomolecules, identifying in seconds the lipid species involved in various CNS pathologies (168)(169). Neurolipidomics has facilitated the development of receptor-independent antipsychotic treatments (RIATs), including LRT.

Lipid replacement therapy (LRT) is a technique which utilizes healthy, natural glycerophospholipids to substitute oxidized components of the plasma membranes lipid bilayer, restoring the physiological fluidity as well as neurotransmitter signaling. This approach, based on the oral supplementation with natural phospholipids and antioxidants, was demonstrated to halt the dissemination of cellular senescence to the neighboring, healthy cells, probably by inhibiting SASP (170)(171)(172)(173)(174). Moreover, LRT was shown to supplant not only cell membranes but also the damaged mitochondrial inner and outer membranes with new and natural lipid species. Indeed, loss of lysophosphatidylethanolamine (LPE), phosphatidylglycerol (PG), and phosphatidylinositol (PI) in senescent mitochondria was shown to cause organelle demise; conversely replacement with healthy lipids promotes mitochondrial thriving (173).

Phosphoinositide-dependent kinase 1 (PDK-1) inhibitors

We surmise that combining LRT with inhibitors of phosphoinositide-dependent kinase 1 (PDK-1), such as Kaempferol, would produce superior results in SCZ compared to LRT alone. Indeed, PDK1 inhibitors reverse cellular senescence, a phenotype previously considered irreversible. Lowered SASP together with the healthy exogenous lipids decrease the risk of peroxidation and ferroptosis (174). Interestingly, Kaempferol is also an antagonist of AhR, a transcription factor and cellular senescence driver. On the other hand, PDK1 activation of protein kinase B (Akt) and glycogen synthase kinase 3 beta (GSK-3β) promotes SCZ pathogenesis (175)(Figure3). The point of contact between exogenously administered phospholipids and PDK1 is phosphatidylserine (PS) which binds PDK1 through its PH domain, blocking PS externalization and the initiation of cellular senescence. Moreover, PH-PS attachment inhibits PDK1 activation of downstream kinases, accounting for the antipsychotic actions of PDK1 inhibitors (176)(Figure 4).

Taken together, LRT inhibits PDK1 as well as Akt and GSK-3β, exerting antipsychotic effects by entirely natural means.

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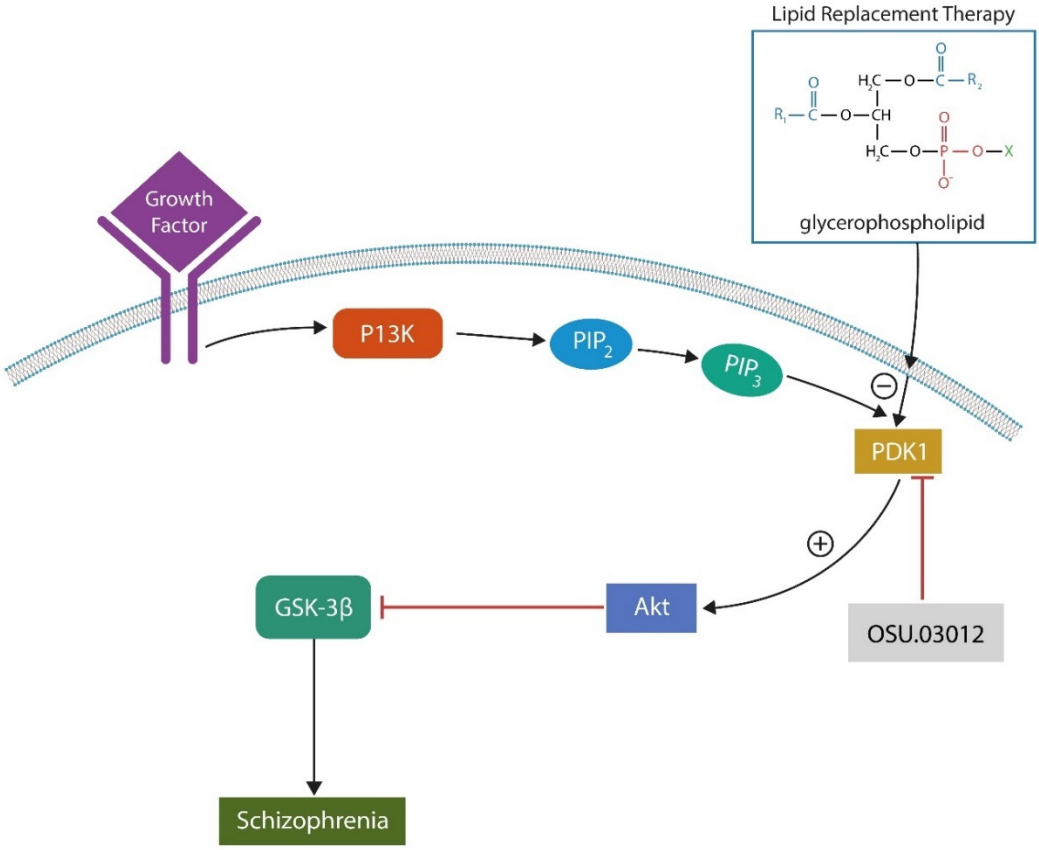

Figure 4. LRT inhibits PDK1 as exogenous phosphatidylserine (PS) binds the PH domain of PDK1, inactivating the downstream kinases, protein kinase B (Akt), and glycogen synthase kinase 3 beta (GSK-3β). LRT and PDK1 inhibitors act as natural antipsychotic agents The novel PDK1 inhibitor, OSU 03012 readily crosses the BBB, enhancing the antipsychotic properties of LRT.

Recombinant human interleukin-22 (IL-22)

Hinting at the microbiome, Emil Kraepelin stated that SCZ was caused by toxins generated in various body regions that could eventually reach the brain, triggering psychosis (66)(177). In addition, the membrane phospholipid hypothesis of SCZ, developed in the 1990s, foreshadowed LRT by predicting that cell membranes can be rehabilitated by exogenous phospholipids (178).

Microbial translocation from the GI tract into the host circulatory system has been proposed over 100 years ago but completely forgotten after Kraepelin's death. Along this line, the "Scientific American" from October 1896, Volume 75, Issue 15, ran the story "Is Insanity Due to a Microbe?", highlighting bacteria-mediated neuropathology, the model supported by the scientists of that time (Figure 5).

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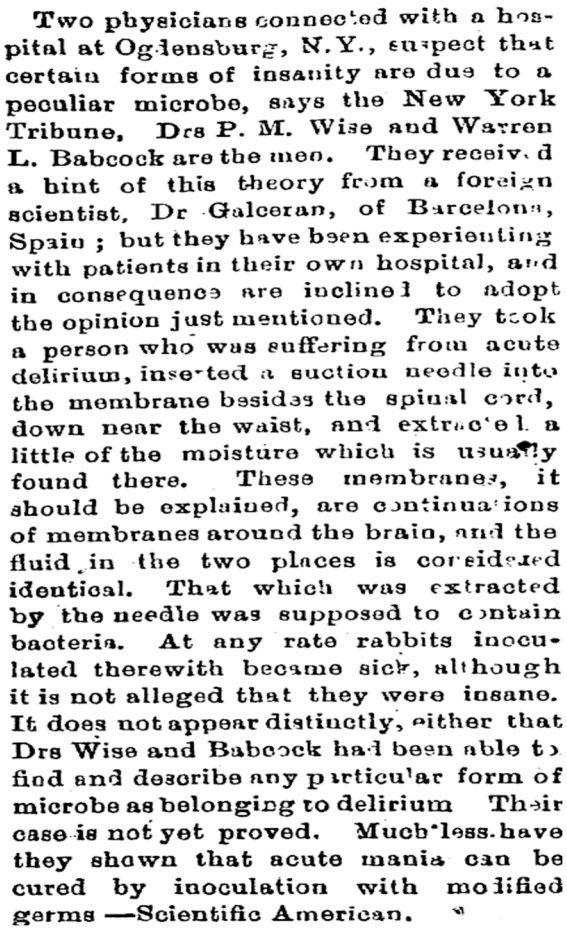

Two physicians connected with a hospital at Ogdensburg, N.Y., suspect that certain forms of insanity are due to a peculiar microbe, says the New York Tribune. Drs P. M. Wise and Warren L. Babcock are the men. They received a hint of this theory from a foreign scientist, Dr Galceran, of Barcelona, Spain; but they have been experienting with patients in their own hospital, and in consequence are inclined to adopt the opinion just mentioned. They took a person who was suffering from acute delirium, inserted a suction needle into the membrane besides the spinal cord, down near the waist, and extracted a little of the moisture which is usually found there. These membranes, it should be explained, are continuations of membranes around the brain, and the fluid in the two places is considered identical. That which was extracted by the needle was supposed to contain bacteria. At any rate rabbits inoculated therewith became sick, although it is not alleged that they were insane. It does not appear distinctly, either that Drs Wise and Babcock had been able to find and describe any particular form of microbe as belonging to delirium Their case is not yet proved. Much less have they shown that acute mania can be cured by inoculation with modified germs —Scientific American.

Figure 5. Endorsed by Emil Kraepelin and other 19th century researchers, microbial hypothesis of. SCZ was forgotten until the arrival of HIV and COVID-19.

During the HIV epidemic of the 1980s, microbial translocation, a common phenomenon encountered in this disease, was linked to virus-depleted IL-22, a cytokine considered "the guardian" of gut barrier (179). The same pathology was reported during the COVID-19 pandemic, emphasizing further that viruses and bacteria can trigger psychosis (180)(181). For this reason, we believe that supplementation with exogenous IL-22 can restore the integrity of gut barrier, ameliorating the symptoms of both SCZ and dementia. Recombinant human interleukin-22 (IL-22), currently being developed as a cancer therapy, is a cytokine known for protecting the biological barriers, iron downregulation, and stimulation of adult neurogenesis, suggesting a beneficial role in SCZ (181).

Aryl hydrocarbon receptor (AhR) antagonists

AhR is a cytosolic transcription factor, initially associated with dioxin toxicity, which responds to numerous endogenous and exogenous stimuli, including xenobiotics (183). In the cytoplasm, AhR is anchored by two molecules of heat shock protein 90 (HSP90) and upon detachment from these chaperones, it enters the nucleus to activate or silence the transcription of many genes. Aside from dioxin, AhR binds several ligands relevant for neuropsychiatry, including DA, serotonin, and clozapine, bringing this receptor into the psychopharmacological arena (184)(185)(Figure 6). In contrast, aripiprazole augments the HSP90 link, preventing AhR dissociation and nuclear entry, evidencing AhR antagonist effects (186).

Dietary AhR antagonists, such as Resveratrol, Luteolin, Kaempferol, Quercetin and the synthetic compounds CH223191, alpha-Naphthoflavone, 6-bromo-3'-nitroflavone, BAY2416964, HBU651, are beneficial by lowering cellular senescence, ameliorating psychosis, and cognition (187)(188). Furthermore, AhR exerts antagonistic pleiotropy (positive effects during the development, and

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detrimental ones later in life). Pleiotropy is responsible for the dioxin property of activating AhR in adulthood, inducing premature cellular senescence and cognitive impairment (189)(190)(191).

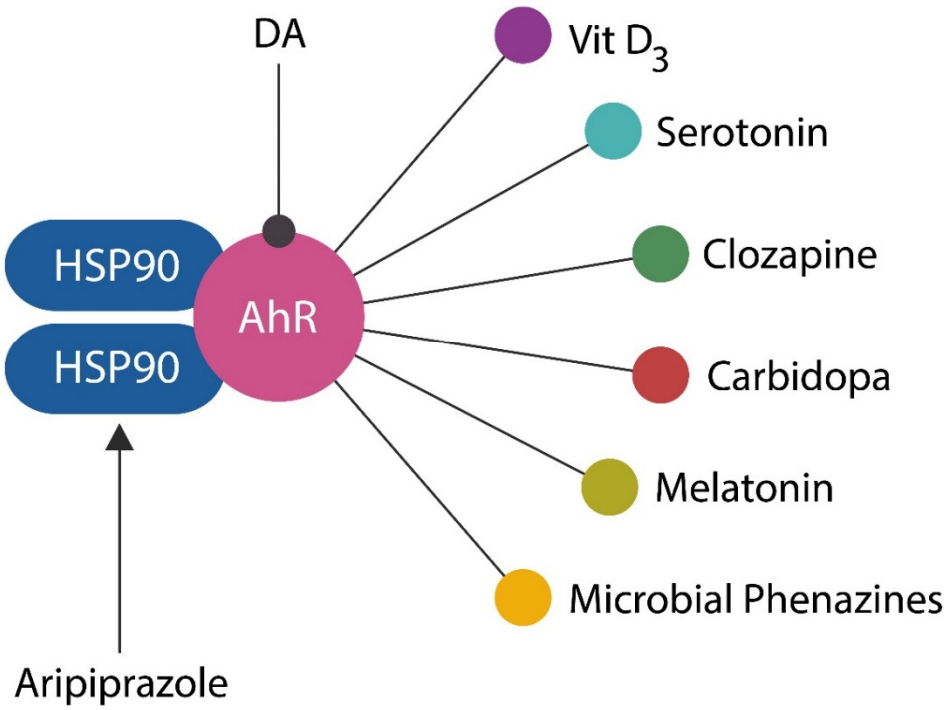

Figure 6. AhR, an upstream receptor for several neurotransmitters, including DA, serotonin, melatonin, vitamin D3, as well as clozapine, carbidopa, and microbial phenazines (natural phenothiazines). Aripiprazole enhances HSP90 attachment to AhR, blocking its entry into the nucleus and the activation of SCZ vulnerability genes.

Conclusions

While acute psychosis responds very well to antipsychotic drugs, chronic psychotic illnesses are much more refractory to these agents. Over the past decades, psychopharmacology has focused excessively on the receptor-dependent actions of antipsychotic drugs and put much less emphasis on the receptor-independent ones, such as antimicrobial and anticancer actions. These are significant for the elimination of translocated microbes and de-escalation of immune responses directed at microbial molecules, such as LPS or mcfDNA. The neglect of noncanonical action mechanisms of antipsychotic drugs over the past decades, has severely limited the development of new models and therapies, leaving chronic psychotic illnesses dependent on the inefficient treatments for acute psychosis.

The long-term exposure to conventional antipsychotic drugs may have detrimental effects on cell membrane lipidome, including peroxidation and intercalation into the lipid bilayer. In return, this may lead to neuronal damage and gray matter loss documented by several neuroimaging studies. To avert neuronal loss by cell membrane damage, elderly with SCZ should receive LRT and PDK1 inhibitors in conjunction with conventional antipsychotics.

Exogenous human recombinant IL-22 protects intestinal epithelia, preventing the microbes or their components from translocating outside the GI tract. This in return averts aberrant immune system activation and the subsequent end-organ damage. Moreover, AhR inhibitors reverse the antagonistic pleiotropy by blocking late-life activation of this protein.

RIATs are likely beneficial for PLWS and comorbid dementia as these conditions are characterized by damaged lipidomes and cell membranes as well as increased intestinal permeability. Elderly forensic detainees in treatment with conventional antipsychotic drugs should receive lipid

supplementation and PDK1 inhibitors to delay the onset of dementia. More studies are needed to evaluate the beneficial effects of these strategies as well as that of iron chelators for restoring cognitive capabilities in forensic detainees and ultimately their capacity to stand trial.

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