Patient Preference and Adherence

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REVIEW

# Phenylketonuria as an Adherence Disease

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**Abstract:** This narrative review explores a novel challenge to adherence in patients with phenylketonuria (PKU). Traditional barriers to maintaining the core of PKU therapy, which involves dietary restrictions, include limited palatability, high costs, difficult access to low-phenylalanine foods, time constraints, and social interference. We propose that adherence may also be hindered by elevated phenylalanine levels in nonadherent patients, leading to cognitive and executive function impairment that reduces their ability to adhere to the diet. Specifically, we hypothesize that the pathophysiological features of PKU create a vicious cycle that exacerbates adherence challenges to the phenylalanine-restricted diet. We therefore propose that PKU may be considered "an adherence disease". The implications of this hypothesis are threefold: 1. Long-term dietary nonadherence is probable among individuals with PKU; 2. the disease itself contributes to the difficulty in adhering to dietary restrictions, potentially alleviating patient guilt; 3. while treatment options depend on individual factors such as disease severity, the most effective approach to mitigating the neurocognitive and psychosocial impacts of PKU is to replace or restore phenylalanine hydroxylase activity.

**Plain Language Summary:**

- Phenylketonuria (PKU) is the most common genetic metabolic disorder. Its management requires adhering to a challenging diet that eliminates phenylalanine to prevent its accumulation in the brain, which can cause significant neurological deficits affecting the patient's quality of life.
- This review focuses on long-term adherence to this diet, as part of a broader investigation into the mechanisms of nonadherence which represents a critical issue in medicine.
- In this article, we propose to consider PKU as an adherence disease—a unique case where the disease's pathophysiology negatively impacts adherence through a vicious cycle, detailed in this review.
- This narrative review is the first to apply general adherence concepts from other diseases to PKU in an interdisciplinary manner.
- Finally, the concept of "adherence disease"—analogous to terms like heart disease— suggests that adherence is a beneficial function prone to failure that can be corrected by understanding its mechanisms.
- This investigation provides strong support for research in gene therapy for PKU.

**Keywords:** executive functions, impulsivity, prospective memory, gene therapy

## Introduction

Phenylketonuria (PKU) is currently the most prevalent hereditary genetic metabolic disorder, with a global incidence of approximately 1 in 10,000 newborns.[1] The majority of PKU cases result from mutations in the *phenylalanine hydroxylase* (*PAH*) gene on human Chromosome 12, inherited in an autosomal recessive pattern. PAH deficiency leads to elevated phenylalanine (Phe) levels. High Phe levels can also be observed in patients with inherited deficiencies of tetrahydrobiopterin (BH4), the cofactor of PAH, or PAH disruption due to the absence of its chaperone DNAJC12.[1–3]

Untreated PKU can manifest in various degrees of severity, ranging from classic PKU (Phe concentration > 1200 µmol/L) to moderate PKU (Phe concentration = 900–1200 µmol/L), mild PKU (Phe concentration = 600–900 µmol/L), and mild hyperphenylalaninemia (HPA) (Phe concentration = 360–600 µMol/L).[4] Elevated Phe levels in patients with untreated PKU can result in major cognitive and neurological deficits, severe intellectual disability, epilepsy, behavioral issues, and visual abnormalities.

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PKU is therefore managed primarily through a diet that restricts Phe, an amino acid found in high-protein foods, to prevent harmful accumulation in the body.[5] Individuals with PKU must avoid or limit foods like meat, dairy, nuts, and some grains, and rely on specially formulated low-protein products and medical foods that provide essential nutrients, including large neutral amino acids (LNAA) supplements. LNAA supplements can help to compete with phenylalanine for transport across the blood-brain barrier, potentially reducing brain phenylalanine levels. Adhering to the PKU diet is challenging due to its restrictive nature, the need for precise dietary management, the limited availability and often high cost of suitable foods and supplements, time constraints, and the social and psychological impacts of maintaining such a strict diet.[6–8] In addition to dietary regimen, pharmacological approaches can be employed. Sapropterin, a synthetic analogue of tetrahydrobiopterin (BH4), enhancing the activity of PAH is one such option.[9] Another alternative involves subcutaneous administration of pegvaliase, an enzyme that facilitates the metabolism of Phe.[10] This can enable individuals with PKU to maintain better metabolic control and potentially allow for a more relaxed dietary regimen.[11] However, its use may be limited by the existence of frequent and serious side effects.[10]

Early initiation of treatment with a Phe-restricted diet can mitigate symptoms, with some patients being asymptomatic,[12] indicating that Phe itself is the primary neurotoxin in PKU,[1,13,14] even if not the exclusive one. However, early-treated PKU patients may still experience cognitive deficits if not well managed later in life, most commonly impacting attention, processing speed, executive functions, working memory, and learning.[12,15,16] Treated patients may also experience psychiatric symptoms such as depressed mood, social withdrawal, generalized anxiety, low self-esteem, and lack of autonomy.[13]

Adherence to diet is therefore of paramount importance in PKU. Nonadherence to long-term therapies is common in all chronic diseases,[17] including PKU, in both children[18] and adult patients.[19] Compared to other chronic diseases, the issue of adherence among individuals with PKU is unique in several ways: first, the diet is the central component of treatment, rather than medication. Additionally, the diet for PKU is different from diets required for conditions like diabetes or obesity, as adherence must take into account factors such as palatability and the cost of replacement foods. Furthermore, PKU manifests at birth, requiring adherence to be managed initially by parents and later by the individuals themselves, including through the challenging period of adolescence. Indeed, the Phe-restricted diet is typically initiated immediately after diagnosis through newborn screening and is initially managed by parents. However, adherence to dietary restrictions often declines after the age of 10 in patients with inborn errors of metabolism on low natural protein diets.[20] This decline is often attributed, at least in part, to the shift in responsibility from primary caregivers to the patients themselves, who are faced with the many challenges involved in adhering to a Phe-restricted diet. However, it has been proposed that patients with PKU may encounter specific challenges in handling their treatment due to the impact of the condition on their neuropsychological status.[20,21] Thus, a significant impediment in tackling psychiatric issues in PKU is that elevated Phe levels may result in symptoms such as depression, anxiety, and attention deficits, hindering individuals' ability to adhere to dietary restrictions, thereby worsening these symptoms.[22]

From these observations, a clear vicious cycle emerges within PKU: 1. Deviation from the prescribed diet leads to an increase in Phe levels; 2. Elevated Phe levels contribute to the deterioration of executive function and memory, as well as increased impulsivity; 3. These neurocognitive impairments further exacerbate nonadherence. Indeed, adherence necessitates intentional processes,[23] and maintaining long-term adherence poses a significant challenge, contributing to nonadherence across various diseases.[24] The presence of a vicious cycle in PKU, as proposed herein, presents a unique challenge for adherence in a chronic disease. A thorough understanding of the mechanisms that lead to nonadherence is important because it could drive the exploration of innovative treatment paradigms.[25] In this narrative review, we first explore adherence to the three aspects of PKU treatment: diet, medications, and follow-up. We then present evidence supporting the three components of the adherence vicious cycle in PKU, suggesting that PKU is also an adherence disease. This leads to the general conclusion that only the restoration of PAH activity, for example through gene therapy, can prevent long-term complications of PKU.

# Aspects of Nonadherence in PKU

## Nonadherence to Diet

In a consensus conference, 100% of experts agreed that the sustainability of medical nutrition therapy worsens from early adolescence onward, making strict adherence to the Phe-restricted diet challenging for most patients and limiting the long-term effectiveness of this therapy in controlling blood Phe concentrations.[26] In a study of 111 adults with PKU, many showed suboptimal adherence to the PKU diet, with 82% consuming natural proteins more and amino-acid supplements less than 4–5 times daily.[27] Among 219 participants, 81.4% consistently adhered to their prescribed diet, while 6.9% partially adhered, and 11.8% did not adhere at all. Children demonstrated higher adherence rates compared to adults. Factors such as lack of medical food, delayed diagnosis, history of being off the diet, and age were significant predictors of psychological comorbidities, with age and history of being off the diet remaining significant in a multivariate model.[28] The higher adherence observed in childhood was also supported by a systematic review focusing on treatment adherence in children and adolescents.[29] Parents of children under 18 were more likely to bring low-protein food from home and request restaurants to accommodate their dietary needs than adult PKU individuals.[30] The impact of age on adherence is extensively discussed in a recent review on factors influencing adherence to the PKU diet.[31]

Following a Phe-restricted diet requires a substantial level of understanding. A United Kingdom nationwide survey with 137 respondents revealed that 43.8% always followed a PKU diet, 28.5% returned to it, and 25.5% were off it. The overall knowledge score was 75.2%, with higher scores in general PKU knowledge than in diet-specific knowledge. Dietary adherence was linked to knowledge, with consistent dieters scoring higher.[32] This highlights the importance of patient education, as individuals with PKU often need to calculate protein exchanges from food labels. A study revealed that over 90% had encountered issues with food labeling in the past six months, finding it confusing.[33] A study on caregivers of children with amino acid metabolism disorders, including PKU, highlighted parent-related barriers like poor self-control, limited medical resources, the diet's burden (restricted choices, tedious preparation, dining out challenges), and limited knowledge.[34]

## Nonadherence to Pharmacological Treatment in PKU

Limited data are available on adherence to sapropterin. In an 86-patient survey, 41 responders were identified, with 29 continuing therapy and 12 discontinuing. There were no significant age or side effect differences between the two groups. Among continuers, 19 used sapropterin consistently, while 10 used it intermittently. Forgetfulness was reported as the primary reason for incomplete adherence by 81% of patients. The main motivation for continuation, stated by 22 patients, was the ability to tolerate more dietary protein.[35] Currently, there is a notable lack of comprehensive data on adherence to pegvaliase therapy. In a recent study, a panel of 11 PKU experts reviewed 18 cases and noted challenges such as side effects and patient adherence.[36] This lack of data is concerning as this treatment mitigates the necessity for protein restriction.

## Nonadherence to Follow-up

Measuring Phe levels helps assess the quality of metabolic control in PKU. Additionally, Phe (or natural protein) tolerance is defined as the amount needed to maintain blood Phe concentrations within a specified therapeutic range.[37] Some patients might experience excessive restrictions, as they actually could potentially elevate their protein intake without a corresponding rise in their Phe levels.[38,39] This highlights the importance of regular monitoring of Phe levels in PKU management. In a survey of 44 clinics in the United States, it was observed that patient adherence to blood Phe testing decreased with age. Among patients aged 30 and older, 37% tested once a year or less. Additionally, 31% of adolescents (13–17 years) also tested only once or twice a year.[19] An online survey of 64 patients with PKU in the United Kingdom revealed that 47% rarely or never conducted home blood tests for Phe levels. Only 9% tested every few months, while 31% tested monthly. The percentage of patients testing fortnightly or weekly was minimal, at 3% and 9%, respectively.[40]

## Nonadherence in PKU: A Vicious Cycle

In the following sections, we provide evidence for three interconnected issues: (1) inadequate adherence to the prescribed diet results in elevated blood Phe levels, (2) elevated Phe levels have a detrimental effect on cognitive function, and (3) this cognitive impairment contributes to further nonadherence to both the diet and medication. These factors create a vicious cycle, suggesting that PKU can be considered an adherence disease (Figure 1). We will also explore how these mechanisms contribute to overweight and obesity, potentially offering new insights into this issue for individuals with PKU.

This hypothesis is supported by a study involving 12 patients that investigated the impact of slow-release large neutral amino acids (LNAAs; 1 g/kg/day) on adherence. The treatment notably reduced the Phe/tyrosine ratio, suggesting enhanced metabolic control. Medication adherence assessed using the Morisky questionnaire revealed a notable improvement. Initially, three patients reported medium adherence, while nine reported low adherence, with 60% achieving full adherence in the past month. By the end of the study, adherence had increased, with 96% achieving full adherence.[41]

### First Arm of the Vicious Cycle: The Impact of Nonadherence to Diet on Phe Levels in PKU

The primary goal of the Phe-restricted diet in PKU is to reduce circulating Phe levels and mitigate its potential toxicity. Therefore, it is not unexpected that nonadherence to diet can compromise this effect. A Cochrane analysis of historical studies on children with PKU found a significant increase in Phe levels following diet termination or relaxation.[42] In a recent study of 30 adult patients with PKU, adherence to the Phe-restricted diet varied. Sixteen patients adhered to the regimen, maintaining low Phe protein intake, while 14 were nonadherent, with an average of 5.4 years without adhering to the diet. Adherent patients maintained Phe concentrations within recommended ranges (120–600 µmol/L), while nonadherent patients had higher concentrations (861 vs 464 µmol/L; $p = 0.002$). Interestingly, nonadherent patients also had a higher body mass index than adherent ones (31.8 vs 24.9 kg/m²; $p = 0.006$).[43] A study involving nine adult patients with PKU who had discontinued their diet showed that reintroducing the diet for one year led to an improvement in cognitive functions.[44]

Furthermore, elevated Phe levels may serve as a predictor for treatment discontinuation. A retrospective study involving 75 children with early-treated PKU aged 7 to 13 revealed a progressive increase in mean blood Phe concentrations with age, most notably between the first and second years. The percentage of samples exceeding recommended Phe levels escalated from 13% in infancy to 67% in early adolescence. Notably, individuals who discontinued follow-ups exhibited higher mean Phe concentrations (360 vs 220.9 µMol/L; $p = 0.004$), particularly during the second year. Blood Phe levels at 12–23 months and 6–8 years significantly predicted discontinuation

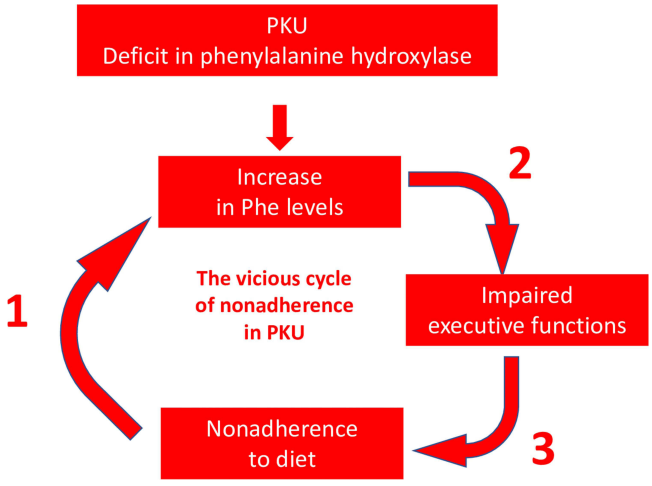


**Figure 1** The vicious cycle of nonadherence in PKU: PKU as an adherence disease.

before reaching the age of 13. In addition, the study observed a rise in the proportion of patients with insufficient annual blood Phe checks as they grew older.[18]

## Second Arm of the Vicious Cycle: The Impact of Phe Levels on Brain Damage and Executive Functions

Individuals with PKU often exhibit abnormalities in brain white matter, which can be assessed using diffusion tensor imaging to evaluate microstructural integrity. A study involving 32 individuals with PKU and 12 healthy controls found that higher Phe levels were linked to significant changes in mean diffusivity in the brain, leading to cognitive performance decline.[45] A retrospective study with 36 children with early-treated PKU confirmed that mean Phe levels, Phe exposure, and the variability of Phe exposure were the key predictors of white matter integrity.[46] However, a study of 30 adult patients with PKU revealed widespread cortical thickness reductions, despite good metabolic control in childhood and adolescence. These changes did not show significant correlations with metabolic parameters or cognitive performance, possibly due to effective metabolic control during earlier years.[47]

There is substantial evidence linking elevated Phe levels to cognitive impairments in individuals with PKU. For instance, a study comparing preschool children with HPA (moderate increase in Phe) and those with PKU (high Phe levels) found that children with PKU had significant impairments in cognitive inhibition, verbal working memory, and visuospatial working memory compared to children with HPA.[48] In a study of 57 adult patients with early-treated PKU, Phe levels increased during adolescence, likely due to relaxed dietary restrictions, showing a significant correlation between intelligence quotient, information processing abilities, and blood Phe levels during childhood and adolescence in older patients.[49] Three meta-analyses have shown a correlation between Phe levels and various cognitive dysfunctions.[12,50,51] A study of 13 children with PKU found significant correlations between overall executive function deficits and tyrosine levels and the Phe/tyrosine ratio, with no correlation with Phe levels due to well-controlled conditions in these children.[52]

It is important to consider not only Phe levels but also their systemic fluctuations, which may arise from the lack of dietary smoothing associated with hepatic PAH deficiency.[53] Two studies in children with PKU suggested that variability in blood Phe levels might have a more significant impact on cognitive functioning than overall Phe exposure.[54,55] Another study involving children with classic (n = 14) or mild (n = 13) PKU indicated that Phe variability was associated with impaired working memory, verbal fluency, inhibitory control, and theory of mind.[56] Finally, a study involving 29 patients with classic PKU revealed a correlation between the Full Scale Intelligence Quotient and Phe levels, but not with their variations. Conversely, 21 patients with moderate PKU exhibited the opposite pattern.[57] Phe levels and their variability may operate through distinct mechanisms: Phe peaks could potentially harm developing brains by affecting white matter integrity, while cumulative Phe exposure, as seen in average levels, could be more detrimental to adult brains due to impacts on neurotransmitter levels.[58]

Interventional studies confirm the relationship between Phe levels and executive dysfunctions. In a study of 10 adult patients with PKU and inadequate metabolic control receiving 12 months of LNAAs (0.8–1 g/kg/day), plasma Phe levels remained stable, while tyrosine levels significantly increased. Psychometric assessments showed improvements in distress, well-being, executive functions, attention, and vigilance, with no noticeable changes in hand dexterity.[59] Although an association does not imply a causal relationship, a short-term (6 months) beneficial effect of BH4 on both Phe levels and white matter integrity was observed.[60] Furthermore, BH4 treatment was linked to enhancements in working memory and brain activation, with neural changes becoming apparent earlier than improvements in working memory performance.[61]

## Third Arm of the Vicious Cycle: The Role of Impaired Executive Functions in Nonadherence to Long-Term Therapies

To understand the impact of cognitive functions on adherence, it is important to acknowledge that nonadherence in chronic diseases often stems from a preference for immediate gratification over long-term health benefits.[62] Therefore, adhering to long-term therapies requires consistent effort based on the patient's logical reasoning, advanced cognitive abilities, and self-regulation. This reliance on intact executive functions enables individuals to control impulsivity and effectively utilize memory to mitigate nonadherence due to forgetfulness.[63]

## Impulsivity and Adherence to Medication and Diet

### The Concept of Intertemporal Choice

Neuroeconomics has highlighted the significance of impatience in compromising the ability to resist immediate temptations in favor of long-term goals.[64] The perceived value of an object diminishes when its acquisition is delayed. Empirical data strongly supports the idea that the devaluation of value (V) can be best represented by a hyperbolic function, such as $V(t) = V(t0)/(1 + kt)$, where "k" denotes a coefficient of impatience or impulsivity that varies among individuals.[65] The decision-making process regarding adherence to chronic disease treatment can be viewed as an "intertemporal choice" between immediate satisfaction and the remote goal of maintaining health. Individuals with a high present bias (a high k value) experience shifts in preferences influenced by the hyperbolic discount function which results in an increase in the perceived value of immediate rewards as they approach. This preference reversal is illustrated in a restaurant scenario: initially, the desire to stay slim outweighs the temptation for dessert, but as time passes, the craving for dessert intensifies, ultimately making it rational to indulge in when presented, regardless of previous intentions.[66] A substantial body of evidence suggests an impact of impulsivity on medication adherence across various conditions, including prediabetes, type 2 diabetes, type 1 diabetes, hypertension, heart failure, asthma, and multiple sclerosis, as well as the initiation of preventive aspirin therapy and hormonal therapy in breast cancer.[67,68] Currently, there is no literature evidence linking time discounting to adherence to diet and/or medication in PKU.

### Adolescence as a Paradigm and the Dual-Brain Argument

Adolescence is a period of life characterized by a high prevalence of nonadherence in chronic diseases such as type 1 diabetes,[69] asthma,[70] and human immunodeficiency virus (HIV).[71] In patients with PKU who receive early treatment, we have seen that Phe levels typically rise from childhood to adulthood.[19,28,31] Additionally, nonadherence during adolescence is a significant predictor of disengagement from follow-up care.[72] Factors contributing to high nonadherence rates include the transition to independent living, social pressures related to food and lifestyle choices, and challenges in maintaining a PKU diet in social interactions with peers.[29] However, this phenomenon may also reflect broader underlying factors. Adolescents are more likely to take risks, with late adolescents showing the highest levels of recklessness, which is probably present from mid-adolescence but only expressed when opportunities arise.[73]

Both nonadherence to recommendations and the tendency for risk-taking observed in adolescence may be attributed to two key traits: impatience, leading to a preference for instant gratification, and disobedience. Research has shown a correlation between acts of disobedience, such as not wearing a seatbelt in the back of a car, and poor adherence to medication regimens.[74] Additionally, reactance, which is the refusal to comply due to perceived restrictions on freedom, is also associated with inadequate adherence.[75] The impatience and disobedience observed in adolescence may have an evolutionary basis; in ancient times, these traits may have encouraged young males to take risks and explore beyond their familial and societal boundaries in search of a mate.[76]

This discussion on adolescent behaviors leads to the dual-brain concept proposed by Casey[76] and Steinberg in 2008.[77] This argument suggests that adolescents' inclination toward risky behavior is due to the uneven development of two brain systems: one focused on seeking rewards and the other on regulating impulses. Risk-taking peaks during adolescence because the socio-emotional system matures early, driving attraction to exciting activities, while the cognitive control system develops more slowly, this disequilibrium resulting in a lack of ability to control hazardous impulses.[78] The competing neurobehavioral decision systems theory by Bickel is another dual-systems model that explains self-control failures by emphasizing the interaction between impulsive and executive decision systems. The impulsive system, involving limbic and paralimbic regions, and the executive system, involving the prefrontal and parietal cortices, are interdependent and compete for control during decision-making.[79] These models are similar to Daniel Kahneman's dual theory of thinking, known as System 1 and System 2.[80] Brain imaging data across different age groups support these hypotheses.[81,82]

### Role of Impulsivity in Overweight and Obesity

Some studies suggest that PKU is often associated with overweight and obesity.[83–86] In the framework of our hypothesis, it is helpful to explore how impulsivity and executive function impairments contribute to weight gain in the general population. A 2016 meta-analysis found a link between elevated delay discounting and increased consumption of unhealthy foods, as well as a higher risk of obesity.[87] Subsequent research indicated that obese individuals show

impairments in executive functions, particularly in inhibition and working memory.[88] Individuals who successfully lost weight demonstrated lower delay discounting compared to obese controls[89,90] and a 2021 meta-analysis identified baseline inhibition and delay discounting as predictors of future weight loss.[91] Household food shoppers with higher delay discounting tend to choose lower-quality, higher-energy foods and beverages.[92] In the NutriNet-Santé Study, impulsivity was linked to higher consumption of low-quality, high-energy foods and beverages while negatively impacting the intake of healthier options.[93] Finally, studies have also shown that obese individuals exhibit greater activation in the right dorsolateral prefrontal cortex during delay discounting tasks.[94]

These findings suggest that impulsivity and working memory deficits contribute to overweight and the consumption of unhealthy foods. It is therefore possible that overweight and obesity in some patients with PKU are not solely due to the low-protein, high-carbohydrate diet but also related to behavioral issues that lead to nonadherence to the prescribed diet aimed at reducing circulating Phe levels. Interestingly, a meta-analysis revealed that the increased prevalence of overweight and obesity compared to that in healthy controls is only observed in classic PKU.[84] Furthermore, the tendency for overweight in PKU primarily affects women.[83] This aligns with a study showing high delay discounting in obese women but not in men,[95] as well as data suggesting higher impulsivity in women than in men.[96]

## Dopamine and Serotonin and Intertemporal Choice

In this section, we will explore how brain deficits in dopamine and serotonin contribute to impulsivity and other executive function deficits. This is particularly relevant in the context of PKU, where PAH deficiency results in elevated Phe levels. LNAAs, including Phe, tyrosine, and tryptophan, compete for transport across the blood-brain barrier through L-type amino acid transporters, which have a high affinity for Phe. Elevated Phe levels saturate these transporters, reducing the entry of other LNAAs into the brain. This, in turn, lowers the availability of tyrosine and tryptophan, impairing dopamine and serotonin synthesis.[97]

### Dopamine and Intertemporal Choice

A study using monetary choice tasks and functional magnetic resonance imaging investigated the Val158Met polymorphism of the *catechol-O-methyl transferase* gene, which affects dopamine degradation. The study found that this polymorphism is associated with impulsive choice behavior and neural activity in the dorsal prefrontal cortex and posterior parietal cortex. Individuals with the 158Met allele, associated with higher dopamine levels, exhibited less bias toward immediate rewards than those with the 158Val allele.[98] Another study by the same research group[99] investigated the impact of acute dopamine depletion in healthy adult males. This depletion was induced by consuming a beverage lacking dopamine precursors. The results showed an increased bias toward immediate rewards in participants with the val/val genotype, indicating individuals with high catechol-*O*-methyl transferase activity and lower baseline brain dopamine levels. Conversely, a single dose of haloperidol was found to mitigate delay discounting by elevating extra-synaptic striatal dopamine levels through blocking presynaptic D2 receptors.[100] In a separate study, striatal dopamine D2/3 receptor (D2/3R) availability and plasma monoamine metabolite levels were assessed in 18 adults with PKU compared to 12 healthy controls. The PKU group exhibited lower levels of homovanillic acid (a dopamine metabolite) and 3-methoxy-4-hydroxy-phenylglycol (a norepinephrine metabolite) along with higher impulsivity levels. Additionally, the PKU group showed higher mean D2/3R availability, suggesting reduced synaptic dopamine levels. Within the PKU group, D2/3R availability positively correlated with impulsivity and error rates on a cognitive flexibility task.[101]

These data provide strong evidence supporting the role of dopamine in delay discounting. Lower dopamine reactivity in the nucleus accumbens core is associated with greater temporal discounting, and studies have shown that lesions in this area lead to higher levels of delay discounting.[102] Expanding on the positive effects of dopamine on patience, researchers have investigated the impacts of tyrosine administration, the precursor of dopamine, on cognitive functions. A meta-analysis[103] has shown that tyrosine supplementation can prevent declines in cognitive task performance, particularly under physically or mentally demanding conditions. This includes tasks such as working memory tasks, multitasking, and convergent thinking, which involves generating a single solution to multiple problems.

### Serotonin and Cognitive Functions

In the brain, L-tryptophan is converted to 5-hydroxytryptophan by *tryptophan hydroxylase types 1 and 2* (*TPH1* and *TPH2*). Subsequent decarboxylation via L-aromatic acid decarboxylase converts 5-hydroxytryptophan to serotonin. Several studies reviewed by Aquili[104] examined the effects of genetic variations in the *TPH1* and *TPH2* genes on brain activity and performance in inhibitory control tasks. One study using the Go/Nogo task found that individuals with the risk allele for *TPH1* had reduced medial prefrontal cortex activity during response inhibition, with no behavioral differences noted.[105] Another study on the 5-choice serial reaction time task revealed that the *TPH2* risk allele (T/T homozygous at the 703 polymorphism) was associated with more premature responses, suggesting inhibitory control deficits linked to reduced input from the ventromedial prefrontal cortex and increased nucleus accumbens response in impulsive T allele carriers.[106] Aquili's review also discussed acute tryptophan depletion, presenting contradictory findings, and concluded that tryptophan and the prefrontal cortex may modulate certain types of response inhibition, cognitive interference, and selective attention, but not reversal learning.

## Memory and Adherence to Medication

The implementation of a long-term treatment regimen involving repetitive actions (such as taking medication) necessitates the engagement of prospective memory, which refers to the ability to remember to perform a task at a later time.[107] This cognitive function relies on the concept of "implementation intention", where individuals set specific cues to trigger actions, such as deciding to take medication. A conceptual model of prospective memory[108] involves several key stages. First, an intention is formed and linked to a specific cue, which can be time-based (eg, "take medication every four hours") or event-based (eg, "take medication after dinner"). Subsequently, an action plan is created, and the cue-intention pairing is established. The second stage includes a delay between intention formation and execution, which may last from minutes to weeks, during which attention may shift to other activities, limiting rehearsal of the cue-intention pairing. In the third stage, the ability to detect and recognize the cue becomes crucial, requiring self-initiated retrieval of the intention. The final stages involve recalling the intention from retrospective memory, which is essential for prospective memory success, and executing the intention, typically an automatic process unless significant neurological deficits like apraxia or aphasia are present.

A 2012 literature review highlighted the role of prospective memory in treatment adherence for various conditions, including HIV, rheumatoid arthritis, and diabetes.[108] A study involving 309 patients with heart failure revealed significant associations between higher attention, executive function, and memory scores and improved medication adherence in unadjusted regression analysis. However, after adjusting for age and minority status, the associations between attention and adherence, as well as executive function and adherence, lost significance. In contrast, the relationship between reduced memory and lower adherence remained significant in the adjusted analysis ($p = 0.008$).[109]

The case of HIV is interesting due to its association, as in the case of PKU, with cognitive impairments affecting memory, processing speed, attention, and concentration.[110] A study using the Memory for Intentions Screening Test and other executive function assessments in patients with HIV infection identified a factor linked to treatment adherence.[111] A 2018 literature review[112] indicated moderate prospective memory deficits in HIV patients, largely independent of common comorbid factors (eg, depression, hepatitis C co-infection) and unrelated to traditional clinical markers of disease severity. These deficits suggest dysregulated strategic processes, such as cue monitoring, consistent with frontal systems pathology and executive dysfunction in HIV-related neural injury. Conversely, more spontaneous and automatic prospective memory processes, relying on less affected posterior brain regions, appeared relatively preserved.

Currently, there is no literature evidence on specific prospective memory in patients with PKU. Several studies have documented deficits in working memory[13,16,113–116] while others have not found differences between clinical and control group in this domain.[51,117]

## Summary: The Impact of Executive Functions, Impulsivity, and Memory on Adherence

Finally, three studies published in a single article aimed to identify common cognitive factors affecting medication adherence across different conditions such as hyperlipidemia, diabetes, and early breast cancer. The studies consistently demonstrated that cognitive function significantly predicted nonadherence, with attention and psychomotor speed being the most reliable predictors. In individuals with hyperlipidemia, mental flexibility and working memory were linked to

adherence to the correct dose and timing over 24 weeks. For patients with diabetes, attention and psychomotor speed were the primary predictors of adherence to prescribed doses. In patients with early-stage breast cancer, attention and executive function were linked to adherence to dosing frequency and inter-dose intervals, while verbal learning and memory were related to adherence over 24 weeks. These findings underscore the consistent influence of specific cognitive functions on medication adherence across diverse medical conditions, irrespective of treatment complexity.[118]

Altogether, these findings support the proposed model in Figure 2, illustrating the relationship between executive functions and adherence to therapies (both diet and medications) in patients with PKU.

This figure illustrates various executive functions that may influence the mental mechanisms underlying nonadherence in patients with phenylketonuria (PKU). The deficiency of PAH characteristic of PKU leads to elevated Phe levels, which in turn has a detrimental effect on executive functions, particularly inhibiting impulsivity control. When impulsivity is not adequately controlled, it hinders adherence to specific treatments for PKU, including dietary restrictions, medication adherence, follow-up appointments, and overall healthy eating habits. This model suggests that impulsivity may also contribute to overweight and obesity in these patients, especially when combined with a high-carbohydrate PKU diet. Inadequate adherence to the PKU diet after starting therapy can result in increased Phe levels, further compromising executive functions and perpetuating a vicious cycle.

## Discussion

A first criticism of the argument presented here is that some of the arguments used are more about medication adherence than dietary adherence. However, adherence extends beyond just medications to include lifestyle changes and any medical prescriptions.[119] Moreover, medication and lifestyle nonadherence are often interconnected. For instance, we demonstrated in a study involving patients with gout that nonadherence to urate-lowering medications was associated with nonadherence to specific gout dietary recommendations and a lack of monitoring uric acid levels, suggesting that nonadherence is a syndrome.[120] Lastly, the role of prospective memory in adhering to a diet is questionable, but it may be involved when taking LNAA supplements, using drugs such as sapropterin or when monitoring Phe levels.

Secondly, the argument for a vicious cycle in PKU presented herein is a hypothesis that requires empirical validation, as it may be no more than a conceptual construct. This hypothesis is based on a narrative review, which is inherently less structured and more susceptible to subjective interpretation than systematic reviews, even though efforts have been made to support each statement with references. Nevertheless, this approach may introduce potential selection biases.

However, this type of review has the advantage of providing a broad understanding of an issue by integrating findings from different disciplines (eg reference to neuroeconomics, comparisons with other diseases) and applying current

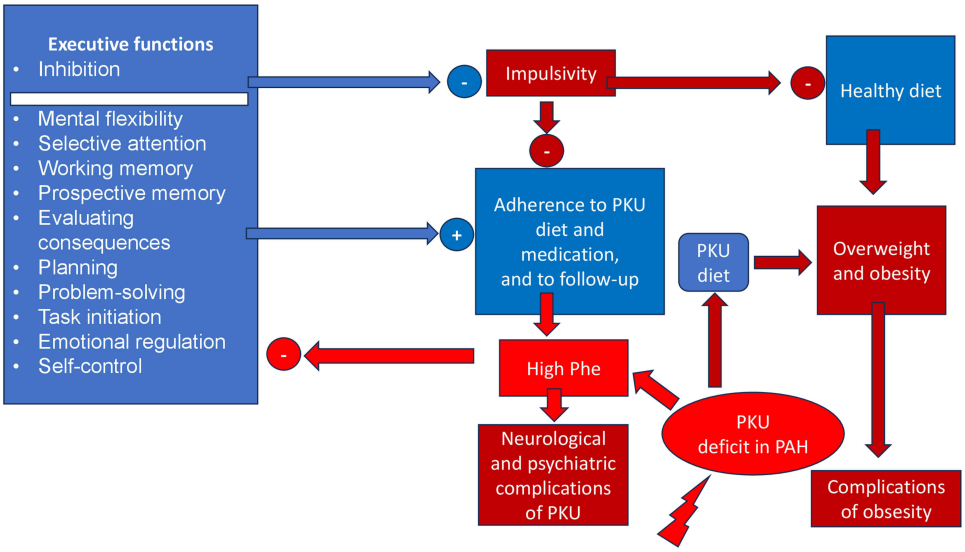


**Figure 2** PKU, Executive functions, impulsivity and adherence in PKU.


https://doi.org/10.2147/PPA.S512719

conceptual frameworks on adherence to a specific disease, PKU, which is novel. It also highlights a number of gaps in the research and the need for further investigation: collection of data on adherence to sapropterin and pegvaliase, specific investigation of time discounting and prospective memory in people with PKU, and consideration of the fact that adherence in the current PKU literature is often assessed by circulating Phe levels (an indirect measure) rather than dietary adherence questionnaires, which could allow real comparisons of adherence levels based on Phe concentrations.

Filling in these gaps can be a first step in the validation of the hypothesis. If the hypothesis is correct, appropriate statistical techniques should be able to demonstrate in a cohort of patients with PKU exhibiting a large range of Phe control the presence of cluster associations[121] between Phe and tyrosine levels and variability, their ratio, BMI, adherence to PKU diet, LNNA, sapropterin and medication for other diseases, impulsivity, prospective memory, and executive functions.

## Conclusion

This novel conceptual framework presents PKU as an adherence disease, with three key implications. First, the existence of a vicious cycle makes dietary adherence a formidable challenge for patients with PKU. Long-term dietary nonadherence is therefore probable among individuals with PKU. Second, the inability to adhere to dietary restrictions is partly a consequence of the disease itself, which could help patients feel less guilty. Lastly, if nonadherence to the diet is a consequence of the underlying PAH deficiency, complete avoidance of neurological and psychological complications in PKU may require restoration of PAH activity (Figure 3).

There are two main approaches to restoration of PAH activity. The first method involves enzyme therapy, such as pegvaliase, which can help manage the condition. However, pegvaliase may pose challenges due to nonadherence issues and severe side effects. The second approach is gene therapy, which holds promise for long-term intervention in PKU.

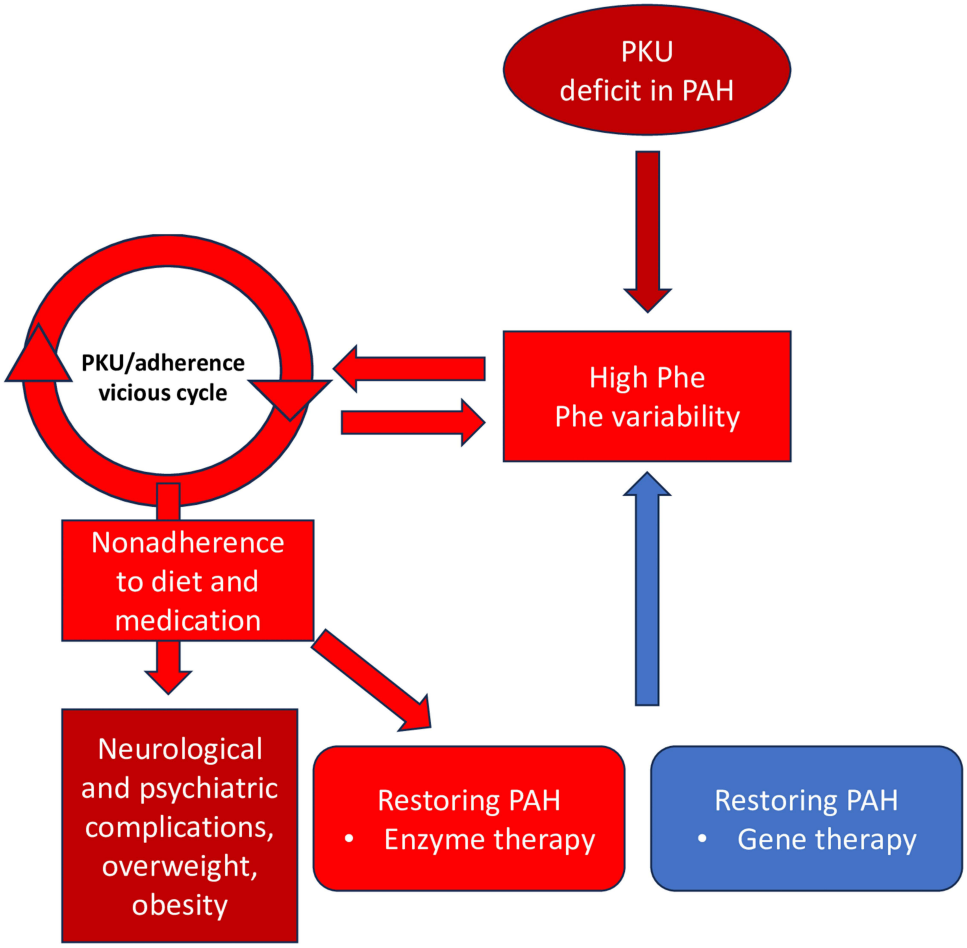


**Figure 3** Restoring Phenylalanine Hydroxylase (PAH) as a treatment for PKU.

A review published in 2024[122,] outlined various methods considered for gene therapy in PKU, including gene addition, delivery of therapeutic mRNA via lipid nanoparticles, gene editing/correction, or gene insertion. A detailed description of these methods is beyond the scope of this article.

Gene therapy in PKU may be the only way to achieve long-term effective intervention in a disease that can potentially lead to a number of neurocognitive deficits altering the quality of life and requires a challenging dietary regimen, with nonadherence causing distress and guilt. The concepts presented here may influence inclusion criteria for these innovative therapies, such as complete PAH deficiency (classic PKU), poor tolerance to phenylalanine leading to high Phe levels with significant variability, uncontrolled disease even with well-conducted treatment, including sapropterin when indicated, documented low adherence to diet and medication and confirmed executive function impairment.

Finally, the concept of "adherence disease"—similar to how we refer to heart disease— proposed herein holds significant implications in the field of adherence. It suggests that adherence can be perceived as a beneficial function which develops in adulthood and is susceptible to failure, but that this failure can potentially be remedied, once its mechanisms are understood. We suggest that PKU might serve as a model for such failure due to the biochemical abnormalities associated with the condition. The pathophysiological insights discussed here could provide valuable understanding of the mechanisms underlying nonadherence in chronic diseases more broadly.

## Disclosure

The author reports personal fees as a speaker at symposia organized by Novo-Nordisk, Abbott-Diagnostics, Lifescan, Bayer-Diagnostics, Mylan-Viatris, Astra-Zeneca, Timkl (lectures on patients' adherence, doctors' clinical inertia, patient education, and hospitality in the hospital); and personal fees as a participant in the scientific boards of Sanofi-Aventis, Targedys and Timkl.

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