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Review Article

# Management of Phenylketonuria

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## ABSTRACT

Phenylketonuria is among the most prevalent amino acid deficiency diseases that affect Americans. Phenylketonuria is an inherited amino acid deficiency disease that causes increased phenylalanine levels, a building block of proteins, in the blood. The condition is prevalent in the United States as it occurs in one out of 10,000 or 15,000 births. Persons with phenylketonuria experience psychiatric disorders, intellectual disability, hyperactivity, behavioral problems, eczema, and neurological issues. A significant percentage of individuals with phenylketonuria do not receive evidence-based care in the United States. Persons with phenylketonuria experience neurological signs, recurrent headaches, tremors, and seizures for failing to complete comprehensive treatment. The research aims to provide detailed information on evidence-based treatment and prevention methods for phenylketonuria to enhance its management and reduce adverse symptoms among phenylketonuria patients. In completing the study, the scholars conducted secondary research that involved nine peer-reviewed articles with accurate and detailed information on phenylketonuria's pharmacological and non-pharmacological treatment methods. The research revealed that enzyme therapy, Large Neutral Amino Acids, sapropterin therapy, dietary therapy, nutrition education, and psychosocial support are essential in managing phenylketonuria among diverse patients. On the other hand, the research found out that scholars have not provided detailed information regarding the side effects of phenylketonuria's pharmacological and non-pharmacological treatment methods. The scholars expect physicians to utilize evidence-based pharmacological and non-pharmacological treatment methods to manage phenylketonuria.

**Keywords:** Phenylketonuria; Enzyme therapy; Neutral amino acids; Sapropterin therapy; Dietary therapy; Nutrition education; Psychosocial support

## INTRODUCTION

Over the years, Americans experience various types of amino acid deficiency diseases that threaten their health and wellbeing. Specifically, phenylketonuria is among the most prevalent amino acid deficiency diseases that affect Americans. According to the United States National Library of Medicine, phenylketonuria is an inherited amino acid deficiency disease, which causes increased levels of phenylalanine, a building block of proteins, in the blood. In the United States, the United States National Library of Medicine indicates that phenylketonuria occurs in one out of 10,000 or 15,000 births [1]. Currently, around 16,000 Americans are living with phenylketonuria. Persons with phenylketonuria experience adverse signs and symptoms, such as psychiatric disorders, intellectual disability, hyperactivity, behavioral problems, eczema, and neurological issues. Bilder et al. note that a study revealed that 53% of adults with phenylketonuria experience intense psychiatric symptoms. Phenylketonuria is a deadly amino acid deficiency disease and it is concerning that its management, treatment, and prevention methods are deficient. Bilder et al. admit that research showed that 7% of adults with phenylketonuria in the United States do not actively receive treatment from metabolic clinics. Medical practitioners do not offer exceptional follow-up care for the few adults with phenylketonuria that receive quality care. It implies that most adults with phenylketonuria experience discontinuation of care. Bilder et al. argue that persons with phenylketonuria experience neurological signs, recurrent

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headaches, tremors, and seizures for failing to complete comprehensive treatment [2]. In this regard, the research identifies and provides detailed information on evidence-based pharmacological, non-pharmacological treatment, and prevention methods for phenylketonuria to resolve the problem and promote phenylketonuria management among Americans.

# LITERATURE REVIEW

The literature review is based on secondary research on online platforms. According to Lew, secondary research involves examining and using existing information to complete studies or literature reviews [3]. The research method allows scholars to collect evidence-based information or data from published reports, e-books, and peer-reviewed journals. The completion of the study is based on evidence-based information from peer-reviewed articles. The researchers resolved to collect and use information from peer-reviewed articles published within the last eight years. The scholars researched online databases, especially Google Scholar and ProQuest, to obtain evidence-based peer-reviewed articles. The researchers used key phrases like "pharmacological treatment methods for phenylketonuria," "non-pharmacological treatment methods for phenylketonuria," "evidence-based treatment methods for phenylketonuria," and "ways of managing phenylketonuria" to obtain adequate peer-reviewed articles to complete the study. The secondary research method enabled the researcher to spend limited time and finances to access detailed and accurate information about managing phenylketonuria.

## Management of phenylketonuria pharmacological and non-pharmacological treatment of phenylketonuria

**Sapropterin therapy:** Cunningham et al. conducted a study to examine the effectiveness of pharmacological treatment of phenylketonuria. In the study, the researchers focused on the efficacy of sapropterin in treating phenylketonuria. According to Cunningham et al., sapropterin is an oral medication that medical practitioners use to reduce elevated Phe levels in phenylketonuria patients. Sapropterin is useful because it increases phenylketonuria patients' tolerance to phenylalanine. In the research, Cunningham et al., [4] showed that sapropterin improved the control of blood Phe levels and increased tolerance to dietary Phe in phenylketonuria patients. The drug enhanced the neurocognitive and psychosocial functions of the phenylketonuria patients in the trial.

Likewise, Peters, Gilder, Dvoracek, and Hegge conducted a study to examine the sapropterin's effectiveness in treating phenylketonuria. In the research, the researchers administered sapropterin to 89 participants. Peters et al. indicate that 56% of the 89 study participants responded positively to the medication. The medication reduced the blood Phe levels of 50 participants by 64%. Peters et al. affirmed that sapropterin is an effective pharmacological treatment for phenylketonuria. Also, Strisciuglio and Concolino completed a study to determine the effectiveness of sapropterin in managing phenylketonuria patients of different age groups. The researcher showed that sapropterin reduced the blood Phe concentrations in adults and children with phenylketonuria by more than 30%. Strisciuglio and Concolino add that sapropterin increased Phe tolerance in different age groups of phenylketonuria patients. Consequently, medical practitioners should utilize sapropterin to manage phenylketonuria's adverse symptoms among children, pregnant women, and untreated or late-treated adults in the United States.

**Large neutral amino acids therapy:** Peters et al. completed research to determine evidence-based treatment options for phenylketonuria. In the study, Peters et al. identified the use of oral Large Neutral Amino Acids as an effective therapy for phenylketonuria. Medical practitioners use oral LNAAs, such as branched-chain amino acids, tryptophan, and tyrosine, for treating phenylketonuria patients. Peters et al. demonstrated that the use of different LNAAs in the study reduced phenylalanine concentration in phenylketonuria patients' blood by 39% from the baseline. Likewise, Al Hafid and Christodoulou conducted a study to review the efficiency of LNAAs in managing phenylketonuria. The research showed that LNAAs treatment reduces cerebral Phe in phenylketonuria patients. For example, Al Hafid and Christodoulou showed that medical practitioners use tryptophan and tyrosine to enhance serotonin and dopamine metabolism among phenylketonuria patients. It implies that LNAAs treatment promotes executive functioning in phenylketonuria patients who fail to comply with the Phe diet. Consequently, medical practitioners should prioritize LNAAs treatment for adult phenylketonuria patients who struggle with adhering to the Phe diet.

Additionally, Strisciuglio and Concolino examined the appropriateness of LNAAs in improving the health outcomes of phenylketonuria patients. In the study, the researchers completed placebo-controlled research to explore the effectiveness of LNAAs. Strisciuglio and Concolino note the placebo-controlled research revealed that LNAAs reduced the Phe concentrations in phenylketonuria patients significantly within fourteen days only [5,6]. LNAA therapy restored large neutral amino acids in brains to promote the neurophysiological functioning of the phenylketonuria patients. As a result, medical practitioners should utilize LNAA therapy alone or combine it with low-Phe diets to benefit phenylketonuria patients.

**Glycomacropeptides therapy:** Al Hafid and Christodoulou completed research to examine the appropriateness of glycomacropeptides in managing phenylketonuria. Al Hafid and Christodoulou define glycomacropeptides as a short protein rich in valine and low in Phe that comes from milk protein. Medical practitioners complement LNAAs treatment with glycomacropeptides supplements to improve the health outcomes of phenylketonuria patients who struggle with adhering to the Phe diet. Al Hafid and Christodoulou state that glycomacropeptides enables phenylketonuria patients to utilize Phe in their blood and retain proteins. For example, Al Hafid and Christodoulou cited a study of the use of glycomacropeptides in PKU mice [7]. The therapy reduced the concentration of Phe in the plasma of PKU mice. Thus, the researchers concluded that glycomacropeptides is an efficient therapy in managing PKU in patients. Equally important, Zaki

et al. completed a study to examine the effectiveness of glycomacropeptides in improving phenylketonuria patients' health and well-being. In the study, the researchers administered glycomacropeptides to 11 phenylketonuria patients for ten weeks. The therapy reduced the levels of Phenylalanine in the blood of 10 out of the 11 phenylketonuria patients. Hence, the researchers concluded that glycomacropeptides are more appropriate in the short-term than phenylketonuria's long-term management [8].

**Enzyme therapy:** Strisciuglio and Concolino completed a study to review enzyme therapy's effectiveness in managing and treating phenylketonuria. Medical practitioners prioritize the use of enzyme therapy when phenylketonuria patients require the introduction of Phe-metabolizing enzymes to reduce harmful high levels of Phe in their blood. Strisciuglio and Concolino admit that clinical trials showed that the combination of enzyme therapy with phenylalanine ammonia-lyase reduced blood Phe in phenylketonuria patients within six days. Al Hafid and Christodoulou examined the benefits of enzyme therapy in managing and treating phenylketonuria. The researchers revealed that the use of enzyme therapy in PKU mice showed reduced Phe plasma levels for several hours. Al Hafid and Christodoulou conclude that enzyme therapy is an effective treatment for phenylketonuria, but patients may require multiple injections of Phe-metabolizing enzymes. Consequently, medical practitioners should prioritize other evidence-based treatment methods to the enzyme therapy in managing and treating phenylketonuria.

Likewise, Rocha and MacDonald reviewed the appropriateness of enzyme therapy in managing and treating phenylketonuria. The study focused on various phases of the trials involving the use of enzyme therapy among phenylketonuria patients. Rocha and MacDonald note that the first phase of tests involved 25 adults that underwent the enzyme therapy procedure. The treatment method reduced Phe concentrations in the blood of five patients by roughly 54%. The patients experienced the side effects of the treatment methods, such as dizziness. Rocha and MacDonald argue that the trial involved around 67 phenylketonuria patients in the second phase. The enzyme therapy reduced the Phe concentrations in all the participants' blood by an average of 65%. Rocha and MacDonald affirm that some patients experienced adverse events, like headache, arthralgia, and fatigue during and after the enzyme therapy. Even though the treatment method has adverse side effects, Rocha and MacDonald conclude that medical practitioners should frequently use enzyme therapy to lower Phe concentrations in phenylketonuria patients.

**Dietary therapy:** Rocha and MacDonald conducted a study to examine the application of dietary interventions to improve health outcomes of phenylketonuria patients. The nutritional interventions for phenylketonuria patients involve three parts: the minimization of the Phe diet, consumption of low-protein foods, and the replacement of non-Phe L-amino acids. Firstly, Rocha and MacDonald state that medical practitioners restrict phenylketonuria patients' dietary treatment to natural proteins [9]. Physicians, nurses, and nutritionists recommend patients to avoid high-protein foods, such as chicken, beef, pork, fish, eggs, and cheese. Rocha and MacDonald indicate that natural protein reduced blood Phe concentrations in phenylketonuria patients. Medical practitioners prescribe natural protein supplements for phenylketonuria patients to compensate for the restricted intake of natural proteins. For example, Castro, Hamilton, and Cornejo argue that medical practitioners prescribe Phe-free formula for phenylketonuria patients to increase their amino acids' levels to promote normal growth and vitamin intake. Rocha and MacDonald add that medical practitioners encourage phenylketonuria patients to consume low-protein foods. For example, nutritionists and nurses expect phenylketonuria patients to consume low-protein pasta or bread to enhance their recovery process and health outcomes. Castro, Hamilton, and Cornejo add that low-protein foods enable phenylketonuria patients to obtain adequate energy levels to promote their growth and minimize their health complications. The consumption of low-protein foods enhances metabolic control of Phe levels and normal brain development among phenylketonuria patients.

## Evidence-based prevention methods for phenylketonuria

Unfortunately, medical practitioners cannot prevent phenylketonuria. Healthcare workers should improve phenylketonuria patients' self-care skills to influence them to adopt healthy behaviors and commit to treatment interventions to overcome adverse signs and symptoms of amino acid deficiency disease.

## Patient education

Singh et al. recommend that medical practitioners and clinical facilities should provide nutrition counseling and education to phenylketonuria patients and their caregivers [8]. Mainly, medical practitioners should educate phenylketonuria patients and their caregivers about the benefits of dietary interventions. For example, they should show patients evidence on the impact of nutritional interventions on retaining healthy blood Phe and overcoming phenylketonuria's signs and symptoms. Singh et al. argue that medical practitioners should educate patients and caregivers about medical foods to manage phenylketonuria. They should assess patient needs and recommend them evidence-based medical foods to support their optimal metabolic control. Castro, Hamilton, and Cornejo state that medical practitioners should educate patients and their caregivers on how to select healthy foods with low Phe. For instance, nutritionists should educate patients above ten years on calculating the Phe content of food to ensure they choose and consume healthy foods with low Phe. The information will help phenylketonuria patients to avoid unhealthy eating habits. Singh et al. indicate that medical practitioners should educate patients and their caregivers on how to track Phe intake. They should provide comprehensive information on counting milligrams or grams of proteins to evaluate patients' Phe intake. Patients will use the information to ensure they only intake appropriate amounts of Phe within specific periods.

### Psychosocial support

According to Singh et al medical providers should offer psychosocial support to phenylketonuria patients and caregivers. Patients require psychosocial support to access community-based care and support to overcome the adverse impacts of chronic physical and mental health problems. Singh et al state that phenylketonuria patients' adherence to treatment diminishes with age and lack of psychosocial support. In the United States, a significant number of phenylketonuria patients do not continue with their treatment because of the lack of psychosocial support. Singh et al say that psychosocial support enables phenylketonuria patients to access appropriate care, understand and adhere to evidence-based treatment methods and medications, and believe that phenylketonuria is a manageable health complication. In offering psychosocial support, Singh et al indicate that medical practitioners should guide phenylketonuria patients and caregivers on how to access modified low-protein foods and medications to address their negative signs and symptoms. They should connect phenylketonuria patients and their caregivers with sources of social support. For example, medical practitioners should guide phenylketonuria patients on how to access mentors and professionals like counselors to help them overcome the disease's emotional and mental complications. Consequently, psychosocial support will promote treatment adherence and quality of life of a significant number of phenylketonuria patients in the United States [10,11].

### Compare and contrast themes and gaps in literature

The common theme in the peer-reviewed journals in this literature review is the treatment methods for phenylketonuria. All the peer-reviewed journals have provided detailed information on either pharmacological or non-pharmacological treatment methods for phenylketonuria. Al Hafid and Christodoulou discussed pharmacological or non-pharmacological treatment methods, such as enzyme therapy, Large Neutral Amino Acids, and dietary therapy. Rocha and MacDonald examined pharmacological or non-pharmacological treatment methods like dietary therapy and enzyme therapy. Rocha and MacDonald reviewed enzyme therapy and Large Neutral Amino Acids. The peer-reviewed journals provide in-depth information on the benefits of the pharmacological or non-pharmacological treatment methods in treating phenylketonuria patients, minimizing the disease's adverse signs and symptoms, and improving patients' health outcomes.

On the other hand, all the peer-reviewed articles do not focus on the themes of the benefits and drawbacks of pharmacological or non-pharmacological treatment methods for phenylketonuria. Some articles provide the pros and cons of individual pharmacological or non-pharmacological treatment methods, whereas other literature only focuses on the benefits. Rocha and MacDonald detail the benefits and drawbacks of enzyme therapy. Rocha and MacDonald affirm that some patients experienced adverse events, like headache, arthralgia, and fatigue during and after the enzyme therapy. On the contrary, Strisciuglio and Concolino provide only the benefits of enzyme therapy in managing or treating phenylketonuria. Consequently, all articles need to provide the advantages and disadvantages of pharmacological or non-pharmacological treatment methods for phenylketonuria.

Essentially, the peer-reviewed articles have gaps that researchers must explore to improve the management of phenylketonuria. Mainly, researchers must explore the side effects of particular pharmacological or non-pharmacological treatment methods for phenylketonuria. Most of the peer-reviewed articles do not have information or recommendation on the effectiveness of pharmacological or non-pharmacological treatment methods in controlling phenylketonuria among particular populations. For example, Strisciuglio and Concolino do not highlight the usefulness or viability of enzyme therapy in managing phenylketonuria among children or pregnant women. Therefore, researchers must address these gaps to enhance the use of pharmacological or non-pharmacological treatment methods, among particular patients with phenylketonuria.

### Questions to further research

- Are there innovative treatment methods for managing phenylketonuria or promoting patients' adherence to phenylketonuria treatment plans or medications?
- Is health informatics essential in promoting treatment and follow-up care among phenylketonuria patients?
- Can medical practitioners utilize Electronic Health Records (EHRs) to promote nutrition education and counseling and psychosocial support among phenylketonuria patients?

Researchers need to consider the three questions in examining evidence-based methods or practices to improve phenylketonuria treatment and management among Americans.

## DISCUSSION AND CONCLUSION

In summation, phenylketonuria is an inherited amino acid deficiency disease that causes increased phenylalanine levels, a building block of proteins, in the blood. The condition is prevalent in the United States as it occurs in one out of 10,000 or 15,000 births. Persons with phenylketonuria experience psychiatric disorders, intellectual disability, hyperactivity, behavioral problems, eczema, and neurological issues. Persons with phenylketonuria experience neurological signs, recurrent headaches, tremors, and seizures for failing to complete comprehensive treatment. In the United States, medical practitioners must use evidence-based methods like enzyme therapy, Large Neutral Amino Acids, sapropterin therapy, dietary therapy, nutrition education, and psychosocial to manage diverse phenylketonuria patients. The evidence-based pharmacological and non-pharmacological treatment methods will help phenylketonuria patients overcome adverse symptoms of health complications and develop healthy behaviors in the long-term.

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## CONFLICT OF INTEREST

The authors have no competing interests to declare.

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