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SYSTEMATIC REVIEW AND META-ANALYSIS

Efficacy and safety of sapropterin dihydrochloride in patients with phenylketonuria: A meta-analysis of randomized controlled trials

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Aims: The aim of the present meta-analysis was to evaluate the efficacy and safety of sapropterin dihydrochloride in phenylketonuria (PKU) patients.

Methods: The following databases were searched for randomized controlled trials (RCT) regarding PKU patients treated with sapropterin dihydrochloride: PubMed, Embase, Cochrane Library and *clinicaltrials*. Two authors independently selected studies, assessed the risk of bias and extracted data. The meta-analysis was performed in RevMan 5.3 provided by the Cochrane Collaboration.

Results: Four studies met the inclusion criteria. In PKU patients with low blood phenylalanine (Phe) concentration, no significant difference was indicated for the decrease of Phe level (weighted mean difference (WMD) = −7.75 μmol L^{-1}; 95% confidence intervals (CI): −82.63 to 67.13, $P = 0.84$, $I^2 = 0\%$), however, the dietary Phe tolerance was significantly improved in the sapropterin group (WMD = 19.89 mg kg^{-1} d^{-1}; 95% CI: 10.26 to 29.52, $P < 0.0001$, $I^2 = 0\%$). In PKU patients with high blood Phe level, sapropterin showed a significant lowering in blood Phe concentration (WMD = −225.31 μmol L^{-1}; 95% CI: −312.28 to −138.34, $P < 0.00001$, $I^2 = 0\%$). There was no significant difference for adverse events.

Conclusions: Sapropterin could bring benefit for PKU patients with high or low Phe level, due to Phe reduction in a short time or dietary Phe tolerance improvement respectively. Sapropterin has an acceptable safety profile.

KEYWORDS

meta-analysis, phenylketonuria, sapropterin dihydrochloride

1 | INTRODUCTION

Phenylketonuria (PKU), characterized by deficient activity of **phenylalanine hydroxylase** (PAH), is a rare autosomal recessive disorder of phenylalanine metabolism. PKU affects approximately 1 in 12 500[1] and 1 in 10 000[2] live births each year in the United States and Europe, respectively. In the chemical reaction of PAH converting phenylalanine into tyrosine, the cofactor tetrahydrobiopterin (BH4) is required.[3] Mutations in the gene encoding PAH results in loss of enzyme activity and Phe concentration elevation in the blood and brain. PKU is classified

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into three main categories according to the severity of hyperphenylalaninemia (HPA): classic PKU (Phe > 1200 μmol L^{-1}), mild PKU (Phe 600–1200 μmol L^{-1}) and mild HPA (Phe 120–600 μmol L^{-1}).[3] Without treatment, toxic Phe concentrations may cause below-average IQ scores[4-6] and severe emotional dysfunction,[7] including attention deficit disorders, epilepsy and behavioural problems.[8]

The basic treatment for PKU is low-phenylalanine diet. It is recommended that diet treatment should be started as early as possible[3] and continued through the whole life.[9] Although a severely restrictive diet is beneficial for PKU patients, long-term compliance is a tough challenge, especially for adolescents and those preparing for or during pregnancy. Sapropterin dihydrochloride (Kuvan®), approved by the US Food and Drug Administration in 2007, may potentially allow a relaxation of diet or even act to completely substitute for dietary intervention. Sapropterin is 6R-BH_4 with biological activity to increase the residual enzyme activity and the stability of the mutant protein.[10] Approximately 25–50% of patients with PAH deficiency are sapropterin-responsive.[11] To prevent potential cognitive function impairment, all patients with blood Phe concentration above 360 μmol L^{-1} are recommended to receive treatment according to the European and US guidelines on PKU. The US guidelines recommend 120–360 μmol L^{-1} as the target Phe level for all patients of any age. Meanwhile, in the European guidelines, target Phe levels vary according to patients' age: 120–360 μmol L^{-1} for patients below 12 years old and 120–600 μmol L^{-1} for patients above 12 years old.[9,10]

Early systematic reviews included only two randomized controlled trials (RCTs).[12,13] With two more RCTs included, we conducted the present meta-analysis to quantitatively assess the efficacy and safety for PKU patients with different Phe blood levels.

What is already known about this subject

- Two previous systematic reviews have demonstrated phenylketonuria patients may benefit from using sapropterin in the short term, with lowered blood phenylalanine (Phe) concentration and increased protein tolerance.

What this study adds

- We conducted a meta-analysis and stratified phenylketonuria patients according to the baseline blood phenylalanine concentration.
- For patients with low baseline Phe level, there was no difference in change of blood Phe concentration between sapropterin and Phe-restricted diet only. However, sapropterin increased dietary Phe tolerance, making partial relaxation of dietary restrictions possible for patients.
- For patients with high baseline Phe level, sapropterin significantly reduced Phe concentration within 6 weeks. As the follow-up period extended to Week 26, there was no difference between the sapropterin and control groups.

2 | METHODS

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[14,15] The study protocol was registered in PROSPERO (CRD42018109725).

2.1 | Search strategy

Studies was systematically searched in the PubMed, Embase, Cochrane Library and *ClinicalTrials* up to 5 September 2018. The following search strategy was used: (kuvan OR phenoptin OR sapropterin OR tetrahydrobiopterin) AND (phenylketonuria OR PKU OR hyperphenylalaninemia OR HPA).

2.2 | Study selection

Eligibility criteria for study selection included: (1) RCTs; (2) patients diagnosed with PKU; (3) oral supplementation of sapropterin (in combination with a phenylalanine-restricted diet or not) compared with no supplementation or placebo; (4) reporting at least one of the following outcomes before and after sapropterin treatment: blood Phe concentration, dietary Phe tolerance, adverse events, which could be extracted from the full text.

Two reviewers independently screened all identified studies and performed the eligibility assessment. Disagreements were solved by consensus between all authors.

2.3 | Data extraction and quality assessment

Using a data extraction form, details of study design, patient characteristics, interventions, control, and efficacy and safety outcomes were independently extracted by two authors. When detailed data were not reported in the publications, the corresponding author was contacted and *clinicaltrials* was visited to obtain additional information. When necessary, GetData Graph Digitizer (Version 2.26) was used to capture the data from figures. Two authors independently assessed the risk of bias of included trials using the Cochrane Risk of Bias tool. Studies are scored as either a low, unclear or high risk of bias in six domains: selection, performance, detection, attrition, reporting and other bias.[16] Differences in data extraction and assessment of bias were solved through meetings.

2.4 | Data synthesis and statistical analysis

Data was analysed using RevMan 5.3 software provided by the Cochrane Collaboration. Subgroup analysis was performed on the basis of the baseline Phe concentration. The overall effect size was

presented as the weighted mean difference (WMD) and 95% confidence intervals (CIs). Heterogeneity was quantitatively assessed by Q-statistic and I^2 index (low heterogeneity: $I^2 \leq 25\%$; moderate: $25 \leq I^2 \leq 50\%$; high: $I^2 > 75\%$). If $I^2 > 50\%$, which was considered as a substantial heterogeneity, a random effects model was implemented to solve the heterogeneity. If $I^2 < 50\%$, the fixed effects model was adopted. Sensitivity analyses were processed when necessary.

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,[17] and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18.[18]

3 | RESULTS

3.1 | Study selection and characteristics of included studies

The process of searching and identifying studies is reported in Figure 1. Four RCTs[19-22] with 307 PKU patients met the inclusion criteria for the meta-analysis. The characteristics of eligible studies are summarized in Table 1. The dose of saproterin ranged from 10 mg kg^{-1} day^{-1} to 20 mg kg^{-1} day^{-1}. Four studies[19-22] reported changes in blood Phe concentration. Two studies[21,22] elaborated dietary Phe tolerance. All studies reported adverse events. Individual RCT appraisal is reported in Figure 2. Three of the studies had a high risk of reporting bias. As to attrition bias, all studies showed low risk.

3.2 | Change in blood Phe concentration

We stratified participants according to the severity of PKU at baseline. Subgroup analysis of patients with low baseline blood Phe level (< 600 μmol L^{-1}) revealed no substantial difference in the change in blood Phe concentration (WMD = −7.75 μmol L^{-1}; 95% CI: −82.63 to 67.13, $P = 0.84$, $I^2 = 0\%$; Figure 3). While subgroup analysis of subjects with high blood Phe concentration (≥ 600 μmol L^{-1}) at baseline showed significant decrease in blood Phe concentration in sapropterin groups (WMD = −225.31 μmol L^{-1}; 95% CI: −312.28 to −138.34, $P < 0.00001$, $I^2 = 0\%$; Figure 3).

3.3 | Change in dietary Phe tolerance

Two studies[21,22] measured the dietary Phe tolerance. Meta-analysis demonstrated that sapropterin significantly improved dietary Phe tolerance (WMD = 19.89 mg kg^{-1} d^{-1}; 95% CI: 10.26 to 29.52, $P < 0.0001$, $I^2 = 0\%$; Figure 4).

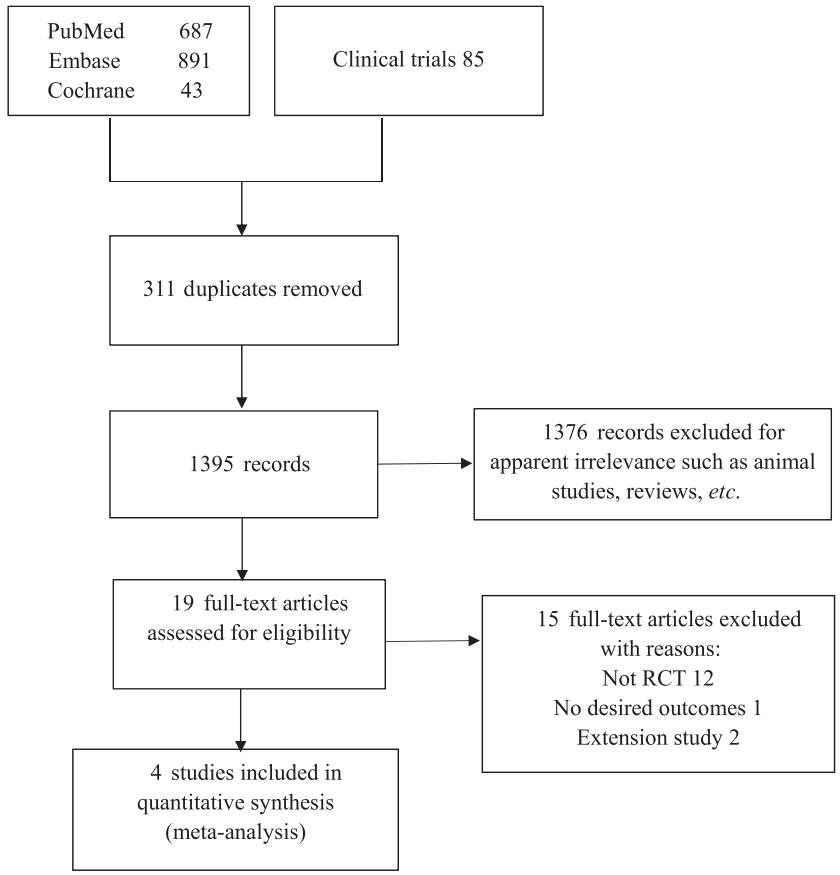

FIGURE 1 Study selection flow diagram

TABLE 1 Characteristics of eligible studies

						Intervention group			Control group		
Author, Year	Trial design	No. of patients (Male/Female)	Age (mean ± SD or range)	Intervention	Dosage (mean or range) (mg kg^{-1} day^{-1})	Mean follow-up (w)	No. of patients (Male/Female)	Age (mean ± SD or range)	Blood phenylalanine concentration, baseline (μmol L^{-1})	No. of patients (Male/Female)	Age (mean ± SD or range)	Blood phenylalanine concentration, baseline (μmol L^{-1})
Levy 2007	RCT, double-blind	88 (51M, 37F)	20.4 ± 9.7 y	Sapropterin vs. placebo	10	6	41 (27M, 14F)	21.5 ± 9.5 y	842.7 ± 299.6	47 (24M, 23F)	19.5 ± 9.8 y	888.3 ± 323.1
Trefz 2009	RCT, double-blind	45 (26M, 19F)	7.5 ± 2.6 y	Sapropterin + Phe-restricted diet vs. placebo + Phe-restricted diet	20	22	33 (20M, 13F)	7.7 ± 2.8 y	275.7 ± 135.2	12 (6M, 6F)	7.1 ± 2.0 y	N/A
Burton 2015	RCT, double-blind	118 (69M, 49F)	19.9 ± 10.1 y	Sapropterin vs. placebo	20	13	61 (38M, 23F)	19.6 ± 10.1 y	680.2 ± 435.4	57 (31M, 26F)	20.2 ± 10.1 y	789.5 ± 465.0
Muntau 2017	RCT, open-label	56 (30M, 26F)	21.2 ± 12.1 m	Sapropterin + Phe-restricted diet vs. Phe-restricted diet only	10–20	26	27 (16M, 11F)	21.1 ± 12.3 m	287.3 ± 166.6	29 (14M, 15F)	21.2 ± 12.0 m	352.9 ± 219.9

N/A, not available; Phe, phenylalanine; RCT, randomized controlled trials; SD, standard deviation; m, month; w, week; y, year.

FIGURE 2 Summary of risk of bias: Review of authors' judgements about each risk of bias for each included study

3.4 | Adverse events

We combined data for common adverse events reported in these four studies, including abdominal pain, diarrhoea, pyrexia, cough, vomiting, upper respiratory tract infection, headache and oropharyngeal pain. Table 2 shows a summary of the meta-analysis of these adverse events. There was no significant difference between groups. No serious adverse events were reported in the studies by Levy et al.[20] or Trefz et al.[22] Another two studies, Burton et al.[19] and Muntau et al.,[21] reported a few serious adverse events (SAEs). However, none of these SAEs was deemed to be related to treatment or led to withdrawals.

4 | DISCUSSION

In this meta-analysis of four studies, we investigated the efficacy and safety of sapropterin compared to a control group with or without Phe-restricted diet. The main findings included: (1) Sapropterin can significantly reduce blood Phe concentration in a few weeks for patients with high Phe level, while in patients with relatively lower blood Phe level, sapropterin shows no significant difference compared with placebo or Phe-restricted diet only. (2) For patients with relatively lower blood Phe level, sapropterin can improve dietary Phe tolerance. (3) Sapropterin shows acceptable safety profile.

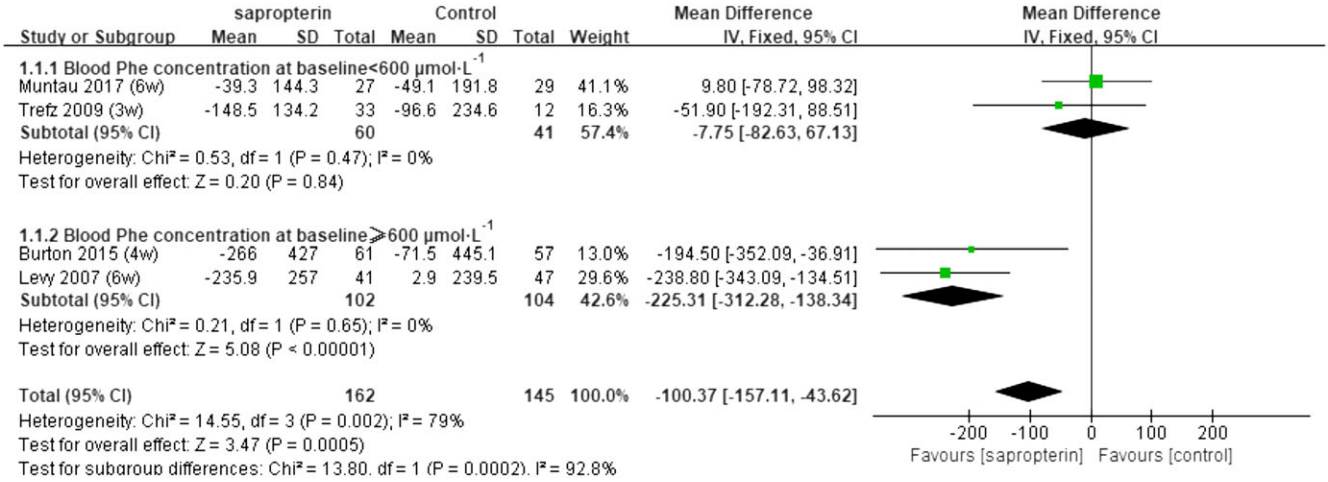

FIGURE 3 Forest plot for the weighted mean difference of change in blood Phe concentration with 95% confidence interval in the fixed effects model

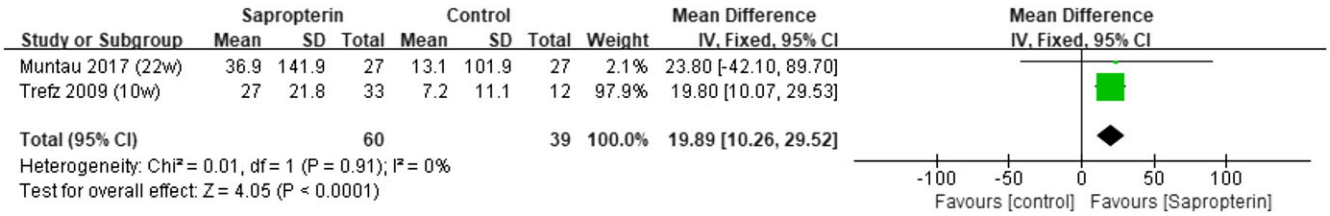

FIGURE 4 Forest plot for the weighted mean difference of change in dietary Phe tolerance with 95% confidence interval in the fixed effects model

TABLE 2 Summary of meta-analysis of adverse events

Outcome	Studies	Participants	Statistical method	Effect estimate	*P*-value	I^2(%)
Abdominal pain	4	395	Odds ratio (M-H, Fixed, 95% CI)	0.80 [0.26, 2.48]	0.70	0
Diarrhea	4	395	Odds ratio (M-H, Fixed, 95% CI)	2.07 [1.00, 4.28]	0.05	0
Pyrexia	4	395	Odds ratio (M-H, Fixed, 95% CI)	0.71 [0.33, 1.53]	0.38	0
Cough	4	395	Odds ratio (M-H, Fixed, 95% CI)	1.01 [0.52, 1.97]	0.97	0
Vomiting	4	391	Odds ratio (M-H, Fixed, 95% CI)	0.66 [0.35, 1.27]	0.22	41
Upper respiratory tract infection	3	339	Odds ratio (M-H, Fixed, 95% CI)	0.58 [0.27, 1.24]	0.16	0
Headache	3	339	Odds ratio (M-H, Fixed, 95% CI)	0.98 [0.58, 1.68]	0.96	0
Oropharyngeal pain	3	339	Odds ratio (M-H, Fixed, 95% CI)	1.07 [0.46, 2.46]	0.88	30

CI, confidence interval; M-H, Mantel–Haenszel

For patients with lower baseline Phe level, there was no difference in change in blood Phe concentration between sapropterin and Phe-restricted diet only. Aggressive treatment may not be necessary because patients can maintain target Phe level through dietary treatment. However, sapropterin increased dietary Phe tolerance, making partial relaxation of dietary restrictions possible. This could help to achieve better compliance to therapy and improve quality of life. This finding supports the results of a prior cohort study.[23] Quality of life was significantly higher in patients with mild PKU under BH_4 treatment as compared to those affected by classic PKU who were under diet regimen. Furthermore, global quality of life scores significantly increased in long treated PKU patients.

For patients with baseline Phe level above 600 μmol L^{-1}, sapropterin significantly reduced Phe concentration within 6 weeks. As the follow-up period extended to 26 weeks, there was no difference (WMD = 95.50 μmol L^{-1}; 95% CI: −67.89 to 258.89, $P = 0.25$) between sapropterin and control group. Therefore, the differences in the change in Phe level from baseline between sapropterin and the control group were greatest at 4 weeks after the initiation of sapropterin treatment and became less pronounced during the 26-week follow-up period.

Several studies[24-29] have shown that when blood Phe concentration exceeds 600 μmol L^{-1}, executive and cognitive function deteriorate. Sapropterin reduced blood Phe concentration to normal range in a short time (within 6 weeks), which might minimize the risk of cognitive impairments.

Two retrospective cohort studies[30,31] with 1–5 years follow-up period compared long-term outcomes between sapropterin and Phe-restricted diet groups. One study of PKU patients under 17 years old collected data over a period of 2 or 5 years. Results showed that there was no significant change between initial and final mean values of Phe levels in both groups. Moreover, the Phe tolerance increased or remained steady in the sapropterin group and the daily intake of natural protein slightly increased at the end of follow-up in the sapropterin group. Similar results of 1-year follow-up was presented in the other study enrolling PKU patients under 4 years. Hence, sapropterin could retain Phe levels in the normal range and improve Phe tolerance in the long run.

There are some limitations to this meta-analysis: (1) Only four RCTs were included and sample sizes were small, which could reduce the reliability of the results. (2) Follow-up periods were short, hence long-term benefit of sapropterin remains unclear. (3) Important outcomes, such as neurocognitive function, nutritional status and quality of life, were not covered, because none of the eligible RCTs reported these outcomes. (4) As all these trials were sponsored by the pharmaceutical manufacturers, potential publication bias may exist.

5 | CONCLUSION

Sapropterin could be beneficial for PKU patients with high or low Phe level due to Phe reduction in a short time or dietary Phe tolerance improvement, respectively. Sapropterin has an acceptable safety profile. Future research with larger sample sizes and longer-term follow-up is still needed to assess the efficacy and safety of sapropterin.

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

J.Q., T.Y., E.W. and M.L. conducted the literature search and study selection, performed data extraction and evaluated study quality. C.C. and L.M. verified quality assessments. J.Q. and T.Y. performed the quantitative meta-analyses and drafted the manuscript with contributions from the other authors. Y.Z. and Y.C. helped in the interpretation of results. Y.C. was responsible for the project and participated in its implementation. All authors read and approved the final manuscript.

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