

# ASSESSMENTS OF EXECUTIVE FUNCTION PERFORMANCE BEFORE AND AFTER SAPROPTERIN TREATMENT IN PATIENTS WITH PHENYLKETONURIA



HTTP://WWW.BMRN.COM/PDF/ASSESSMENTOFEXECUTIVEFUNCTIONPKUV6.PDF

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## INTRODUCTION

Phenylketonuria (PKU) has been associated with neurocognitive deficits possibly due to: (1) the direct effects of hyperphenylalaninemia, (2) the indirect reduction of neurotransmitter and (3) defective protein synthesis, (4) white and grey matter anomalies and/or (5) oxidative stress caused by a defective phenylalanine hydroxylase (PAH) enzyme. It has been reported that children with PKU who are treated early and continuously with a phenylalanine (Phe)-restricted diet and/or have lowered blood Phe, have improved neurocognitive outcomes.

Sapropterin (KUVAN<sup>®</sup>, BioMarin Pharmaceutical Inc., Novato CA USA), a synthetically-prepared salt of naturally occurring tetrahydrobiopterin (BH4) and a co-factor for PAH, is known to reduce blood phenylalanine (Phe) in BH4-responsive patients [2]. Sapropterin treatment is associated with improvements in both working memory and brain activation [3]. It is not known if sapropterin is associated with improvements to other executive function domains in patients with PKU.

The executive cognitive functions are a collection of mental processes responsible for purposeful, goal-directed, problem-solving behavior [1]. The Behavior Rating Inventory of Executive Function<sup>®</sup> (BRIEF) assessment measures the extent to which a respondent reports problems with the various domains of executive functioning (e.g., Inhibit, Shift, Emotional Control, Self Monitor, Initiate, Working Memory, Plan / Organize, Task Monitor, Organization of Materials). BRIEF is a reliable and validated diagnostic tool for the evaluation and treatment of executive control dysfunctions when used in conjunction with psychological, neuropsychological, and other clinical assessments.

## METHODS

A retrospective chart review was performed using data from twenty-nine (29) patients with PKU at the PKU Program and Metabolic Screening Coordination Centre for New Brunswick, Moncton, New Brunswick, Canada and at the Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago IL, United States. For patients in New Brunswick (Moncton Clinic), blood Phe is collected at home or during clinics using capillary blood directly deposited on filter paper cards. These are sent out by mail to the IWK Health Centre Lab in Nova Scotia for analyses using Tandem Mass spectrometry. For patients in Lurie Children's Hospital, blood samples for blood Phe are collected at home or during clinic using capillary blood directly deposited on filter paper cards. The filter cards are sent to a laboratory and analyzed using ion chromatography.

All patients were tested, by self-evaluation and/or by evaluation by an informant, using a BRIEF assessment and some patients had multiple assessments. After the screening test(s), sapropterin was administered a dosage of 10-20 mg/kg per day (mean: 19.6 mg/kg/day) to each patient (according to the standard of care) before patients were again evaluated with a final BRIEF assessment. Some patients had multiple pre- and post-sapropterin BRIEF assessments and not all sub-assessments were conducted with each patient. All BRIEF T-scores were adjusted for age and gender. BRIEF scores ≤ 50 are considered normal, scores > 50 ≤ 65 are considered indicative of mildly elevated and areas of concern, and scores > 65 are considered abnormally elevated and clinically significant<sup>1</sup>.

Pre-sapropterin and post-sapropterin BRIEF sub-assessment percentile scores were compared and significance was assessed by paired t-test. For correlation of self-reported vs. informant-reported scores and their corresponding differences, a two sample t-test was performed. For factor analysis, a regression analysis was performed. P-values < 0.05 are considered significant.

Table 1. Subject Data Demographics

Demographic	Values/ Mean ± SD (Range)
Gender	Female N=13 Male N=16
PKU Type (by blood Phe)	Classic (> 1200 µmol/L) N=18 Not Classic (600 - 1200 µmol/L) N=4 Hyperphenylalaninemia (< 600 µmol/L) N=5 Unknown N=2
Age at Sapropterin Screening	22.5 ± 11.2 (Range: 4 to 47 years)
Baseline Phe pre-sapropterin	781 ± 464 µmol/L (Range: 103 to 1678 µmol/L)
Median Phe post-sapropterin	622 ± 393 µmol/L (Range: 145 to 1518 µmol/L)
Duration of sapropterin exposure between date of screening test and date of final BRIEF test	203.6 ± 161.9 days (Range: 22-721 days)

## RESULTS

Table 2 and Figure 1 shows the averaged BRIEF results of the pre-sapropterin, post-sapropterin, and the difference between the two mean scores. Most of the differences were statistically different and some of the subjects showed improvements up to 50 percentile points while others showed declines in the post-sapropterin percentiles of up to 18 percentile points. The overall average delta percentile was -4.0 ± 1.7 percentile.

Table 2. Summary Statistics for BRIEF Study. Significant p-values are highlighted.

Assessment	Pre-Sapropterin BRIEF Percentiles Mean ± SD (N) (Range)	Post-Sapropterin BRIEF Percentiles Mean ± SD (N) (Range)	Delta Percentiles Mean ± SD (N) (Range)	p-value
Inhibit	51.9 ± 13.4 (41) (36 to 86)	47.2 ± 7.4 (38) (36 to 66)	-4.2 ± 10.1 (35) (-31 to 11)	<b>0.0188</b>
Shift	51.6 ± 11.7 (41) (38 to 91)	47.4 ± 9.9 (38) (35 to 83)	-3.1 ± 8.5 (35) (-22 to 13)	<b>0.0409</b>
Emotional Control	51.4 ± 11.7 (41) (37 to 86)	49.3 ± 10.2 (38) (38 to 75)	-1.1 ± 7.9 (35) (-29 to 12)	0.4200
Self Monitor	50.9 ± 12.3 (36) (37 to 81)	47.5 ± 10.1 (33) (37 to 72)	-2.4 ± 6.6 (30) (-17 to 11)	0.0528
Behavioral Regulation Index	51.9 ± 12.6 (41) (37 to 92)	47.8 ± 9.4 (38) (35 to 74)	-3.1 ± 7.5 (35) (-27 to 9)	<b>0.0215</b>
Initiate	54.0 ± 14.0 (41) (37 to 91)	47.5 ± 10.7 (38) (35 to 86)	-7.2 ± 10.1 (35) (-33 to 17)	<b>0.0002</b>
Working Memory	59.0 ± 14.8 (41) (40 to 95)	52.2 ± 11.4 (38) (38 to 91)	-6.6 ± 10.9 (35) (-33 to 8)	<b>0.0011</b>
Plan / Organize	53.2 ± 12.6 (41) (37 to 94)	49.1 ± 10.1 (38) (33 to 80)	-4.1 ± 10.5 (35) (-32 to 18)	<b>0.0273</b>
Task Monitor	50.9 ± 13.6 (36) (36 to 88)	46.4 ± 9.5 (33) (33 to 79)	-3.8 ± 8.8 (30) (-20 to 14)	<b>0.0250</b>
Monitor	49.5 ± 13.0 (20) (32 to 93)	47.6 ± 9.1 (19) (36 to 68)	-3.2 ± 13.9 (17) (-50 to 12)	0.3509
Organization of Materials	49.8 ± 8.0 (41) (36 to 70)	48.6 ± 8.2 (38) (36 to 70)	-2.4 ± 7.6 (35) (-16 to 13)	0.0734
Metacognition Index	54.4 ± 12.9 (41) (38 to 91)	49.0 ± 9.9 (38) (35 to 81)	-5.9 ± 9.3 (35) (-33 to 13)	<b>0.0007</b>
Global Executive Composite	53.5 ± 13.2 (41) (39 to 95)	48.1 ± 9.7 (38) (34 to 78)	-5.1 ± 8.8 (35) (-29 to 11)	<b>0.0017</b>

Figure 1. Average ± SD BRIEF<sup>®</sup> Assessment Scores for Patients with Phenylketonuria (N=38) Before and After Sapropterin Exposure (T-scores < 50 are normal and T-scores > 65 are clinically significant)

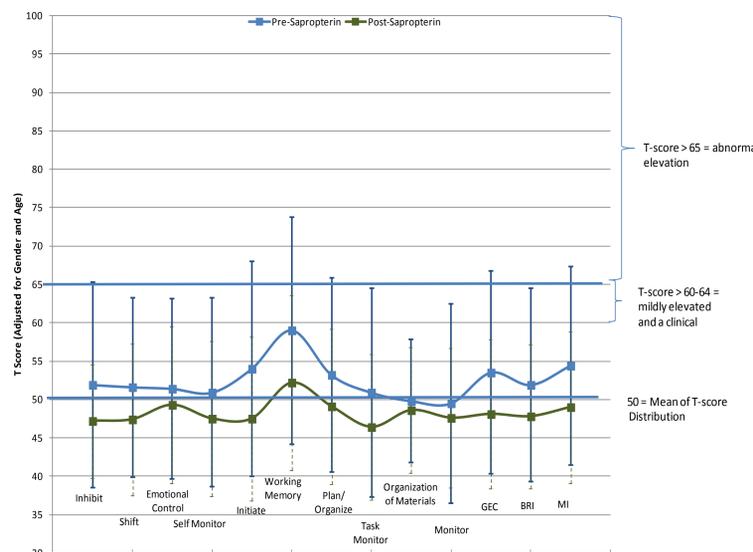


Table 3 shows a regression analysis using the factors of: (1) age, (2) duration of sapropterin drug exposure, (3) Pre-Phe, (4) Post-Phe, and (5) PKU severity as factors to each predict changes in BRIEF score delta percentiles. Only two of the factors showed significance for two separate sub-assessments and the preponderance of the regression factors were not significant.

Table 3. P-values for one factor analysis of Age at Screen, Duration of Exposure, Pre-sapropterin Phe, Post-sapropterin Phe, and PKU severity. Significant P-values, two indices and one summary composite are highlighted.

Assessment	p-value (Age at Screen)	p-value (Duration of Kuvan Exposure)	p-value (Baseline Phe before Kuvan)	p-value (Median Phe level after Kuvan)	p-value (PKU Type)
Global Executive Composite	0.5483	0.2795	0.1851	0.3806	0.7539
Behavioral Regulation Index	0.2901	0.0770	0.3346	0.4991	0.1622
Inhibit	0.3739	<b>0.0246</b>	0.0702	0.1324	0.2174
Shift	0.1911	0.7104	0.7265	0.9575	0.3486
Emotional Control	0.4064	0.1017	0.9336	0.9642	0.1107
Self Monitor	0.2559	0.1682	<b>0.0568</b>	0.0842	0.1824
Metacognition Index	0.4170	0.7922	<b>0.0323</b>	0.0638	0.9737
Initiate	0.8908	0.5686	0.0675	0.1777	0.8016
Working Memory	0.2703	0.6689	0.4566	0.8720	0.6394
Plan / Organize	0.7197	0.3816	0.3020	0.4432	0.8003
Task Monitor	0.5981	0.2811	0.0558	0.1354	0.8030
Organization of Materials	0.1705	0.6300	0.0562	0.0959	0.2126
Monitor	0.3074	0.9295	0.8664	0.9920	0.8725

## OUTCOMES PER PKU SEVERITY

Subjects with non-classic/other PKU showed general improvement in post-sapropterin Global Executive Composite BRIEF scores (range: 2 to -27 percentile changes, N=10). Ten subjects with classic PKU also showed improvements in post-sapropterin Global Executive Composite BRIEF scores (range: -3 to -29 percentile changes, N=10), whereas seven others with classic PKU did not show improvement in post-sapropterin Global Executive Composite scores (range: 0 to 11, N=7).

## CONCLUSION

The data suggests that sapropterin at a mean dose of 19.6 mg/kg/day is associated with improvements in executive function domains in patients with PKU when evaluated using the BRIEF assessment.

- The data show a consistent pattern of generally higher pre-sapropterin BRIEF scores and generally lower post-sapropterin BRIEF scores for each of the cognitive domains (Figure 1).
- The average post-sapropterin BRIEF assessment showed clinical improvement (average percentile range: -1.1% to -7.2%). However, specific patients with PKU show up to a 50% improvement in certain executive function scores after taking sapropterin (Table 2).
- Impairments of executive function are one of the most consistent findings of persons with PKU [4]. Sapropterin treatment might be useful for some individuals with PKU to optimize care and improve quality of life.
- Except for Inhibit (significant for duration of sapropterin exposure) and Metacognition Index (significant for baseline Phe pre-sapropterin), the results were not significantly affected by any one single factor: i.e., age at screen, duration of sapropterin exposure, pre-sapropterin Phe, Post-sapropterin Phe, or PKU type (Table 3). This suggests that some other factor (or combination of factors) predict sapropterin patient benefit.
- Further research is warranted on lifetime Phe exposure, longer duration of sapropterin exposure, index of dietary control, and/or the type of patient with PKU whose executive function is likely to benefit from sapropterin treatment – especially because some patients with classic PKU showed a post-sapropterin benefit in their Global Executive Composite scores.

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