

# Suboptimal provision of medications and dietary products for phenylketonuria in Malta

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## Abstract

In Malta phenylketonuria (PKU) is mostly due to dihydropteridine reductase (DHPR) deficiency rather than phenylalanine hydroxylase deficiency (classical PKU), and is associated with long term neurodisability in all affected patients. The absence of newborn screening for PKU in Malta results in a later diagnosis and an increased burden on families and affected individuals. This burden is further compounded by problems in adherence to strict low-phenylalanine diets, in part due to problems dispensing appropriate amounts of low-phenylalanine products and, in those with DHPR, the regular provision of neurotransmitter and cofactor supplementation. Over a 6.5-year review, complete provisions were dispensed in 68% of all prescriptions for L-dopa, 67% for 5-hydroxytryptophan, 63% for low protein food, 61% for folic acid and just 30% for low protein drinks. The problems encountered in the management of PKU highlight similar problems facing those with other rare, metabolic or 'orphaned' diseases. Yet some of these problems, particularly with regard to the dispensing of medicines and special food products can be reduced or eliminated. This would require a radical and comprehensive overhaul of the funding, procurement, stocking and dispensing of all pharmaceutical provisions in order to achieve stable phenylalanine levels throughout childhood and through to later life.

## Keywords

phenylketonuria, suboptimal provision, Malta

## Introduction

Phenylketonuria (PKU) is a rare condition affecting approximately 1 per 10-19,000 of most populations studied, and several subtypes exist.<sup>1-2</sup> The more uncommon atypical form resulting from dihydropteridine reductase (DHPR) deficiency<sup>2</sup> appears to be most prevalent in Malta, and it has been estimated that up to 3.3% of the population may carry the abnormal gene mutation for this condition.<sup>3</sup> Despite this high carriage rate, phenylketonuria is not yet screened for at birth and presents late, although the case for routine newborn screening for PKU at a national level was made as early as 2005.<sup>4</sup> The burden of PKU in childhood in Malta has been recently reviewed by Attard and Attard Montalto.<sup>5</sup> The spectrum of PKU-related medical complications including significant neurodisability in all affected individuals, the daily requirements of medication and food alternatives, complex management and the psychosocial, educational and financial burden of PKU on patients, their families and Health services has been described in detail.<sup>5</sup>

Five of the six children diagnosed with PKU in Malta since 1996 suffer with DHPR deficiency and, for them, dietary manipulation is insufficient and they require daily medication with dopamine-pathway analogues and cofactors including L-dopamine, 5-hydroxytryptophan, folic acid as well as low protein food products and low or phenylalanine-free drinks/milk.<sup>6-7</sup> The short half-life of these medications necessitate dosing four to five times daily and delays in treatment of just a few hours is rapidly followed by neurological symptoms such as dystonia, irritability and behavioural changes.<sup>7</sup> The requirement for regular and timely medication to sustain steady-state conditions is paramount and poses yet another challenge to the day-to-day burden of PKU.<sup>8</sup> Ideal medical control can only be achieved by patient and

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parent cooperation together with an efficient provision of all therapeutic requirements. The latter cannot be under-estimated and this study, a qualitative phenomenological case-based review of patient experiences, was designed to review this crucial aspect in the management of these children.

### Methods

All children below the age of 16 years with any form of PKU were identified over a twenty-year period, from 1996-2015. For those still resident in Malta in 2015, their official 'yellow' pharmacy-issued and updated cards were analysed for the preceding six and a half-year period, when Paediatric Services migrated to the new national hospital. All PKU-related prescriptions including medicines, food products and special milks/drinks, were identified and assessed for quantity dispensed. Routinely, and in accordance with the prevailing hospital policy at the time, these medications and provisions were supplied and dispensed for a two-month period. Hence, any dispensed medication that provided adequate provisions for the next two months was taken to represent 100% for that individual prescription. Anything less (or more) was calculated as a percentage of the 'standard' two-month allowance, and this exercise was performed for all PKU prescriptions over the 6.5-year period, January 2009 - June 2015.

### Results

Over a twenty-year period from 1996-2015, five patients with PKU due to DHPR and one patient with classical PKU due to phenylalanine hydroxylase deficiency were diagnosed in Maltese children. Of these, three siblings with DHPR deficiency emigrated and prescriptions were analysed for the remaining three patients. Two boys with DHPR deficiency required regular medication with L-dopamine, 5-hydroxytryptophan and folic acid, whilst both patients required low protein food and low/free phenylalanine milk/protein drink substitutes. The third patient with classical PKU was diagnosed midway through the study period and required low protein food and low/free phenylalanine milk but no dopamine pathway analogues. This study showed that, over a 6.5-year period, 456 prescriptions were issued for PKU-related products. Of those, 412 were for the two patients with DHPR deficiency, with just 9.5% for milk and food products for the girl with classical

PKU. If all prescriptions that were issued covered 100% of the patients' requirements in all cases, there should have been approximately 430 item-prescriptions for these three patients in the same time period, averaging 30 each per annum (p.a.) for those with DHPR, and 12p.a. for classical PKU. In practice, DHPR patients were issued with 31.7 prescriptions p.a. (median 31,  $SD\pm 5.1$ ), and one patient with classical PKU received 12.3 prescriptions p.a. (median 12,  $SD\pm 0.5$ ). Table 1 shows the breakdown of the individual prescriptions, and confirms that the main contributor to the 5.8 % 'above estimate' prescriptions arose due to repeat/extra prescriptions for low protein drinks.

*Table 1: Prescriptions according to pharmaceutical item over 6.5 years*

Prescribed item	Estimated number of prescriptions	Actual number of prescriptions
L-dopamine	78	56
5-hydroxytryptophan	78	80
folic acid	78	70
Low protein food	78	84
Low protein drinks*	98	130
Phe-free protein milk**	20	36

*\*Required for all patients; \*\* only for young girl with classical PKU, diagnosed half way through study period.*

The child with classical PKU did not require medication, was diagnosed more than half way during the study period and, for this patient, data was incomplete and was not included in subsequent analyses. For the two boys with DHPR, further breakdown of the actual amounts dispensed compared with what was prescribed for a two-month period, showed that all PKU medications were intermittently or frequently supplied in inadequate amounts. As shown in Figure 1, L-Dopa was insufficiently dispensed in 32% of prescriptions, 5-hydroxytryptophan 33%, folic acid in 39%, low protein food in 37% and PKU cooler (low protein drink) in 70% of all prescriptions. Figures 2A-E show the spread of prescriptions for each individual item over a 6.5-year period, and highlight the frequency of incomplete amounts dispensed relative to the prescribed two-monthly supply. Suboptimal

dispensing averaged approximately one third of all prescriptions for most items, with low protein drinks being consistently unavailable in sufficient

quantities and, therefore, not dispensed 'in full' for more than two thirds of the time.

Figure 1: Frequency (as %) of complete PKU items dispensed over 6.5 years

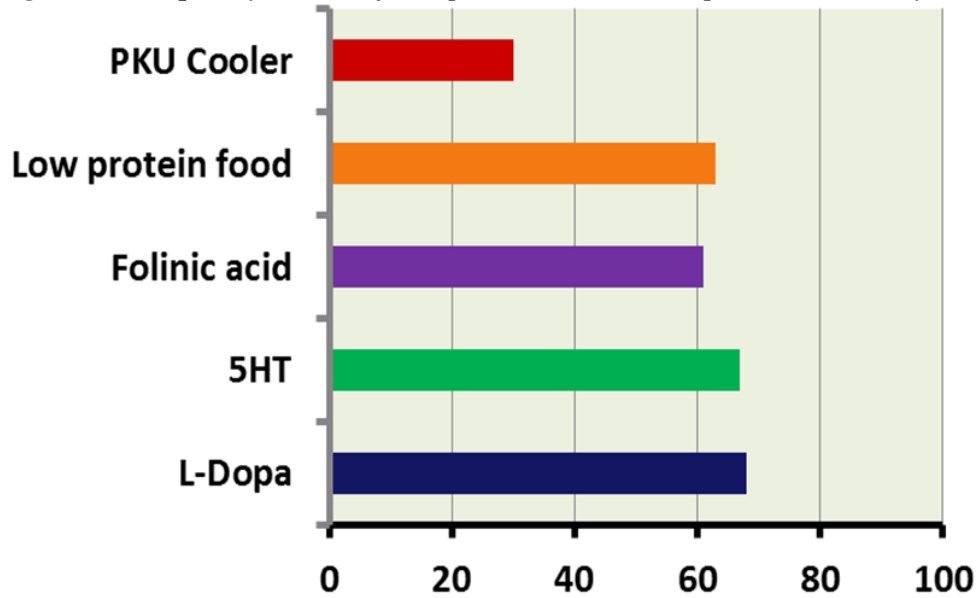


Figure 2A: L-dopa

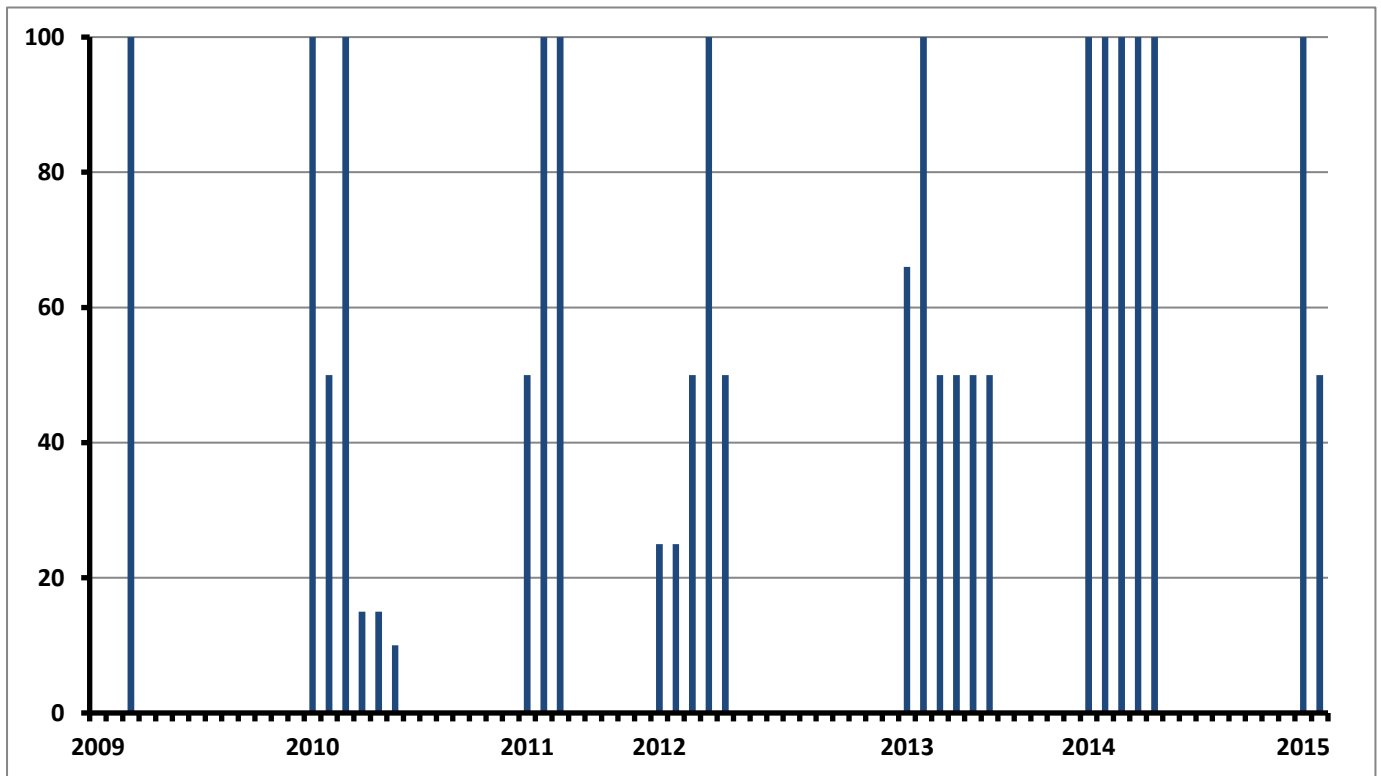


Figure 2B: 5HT

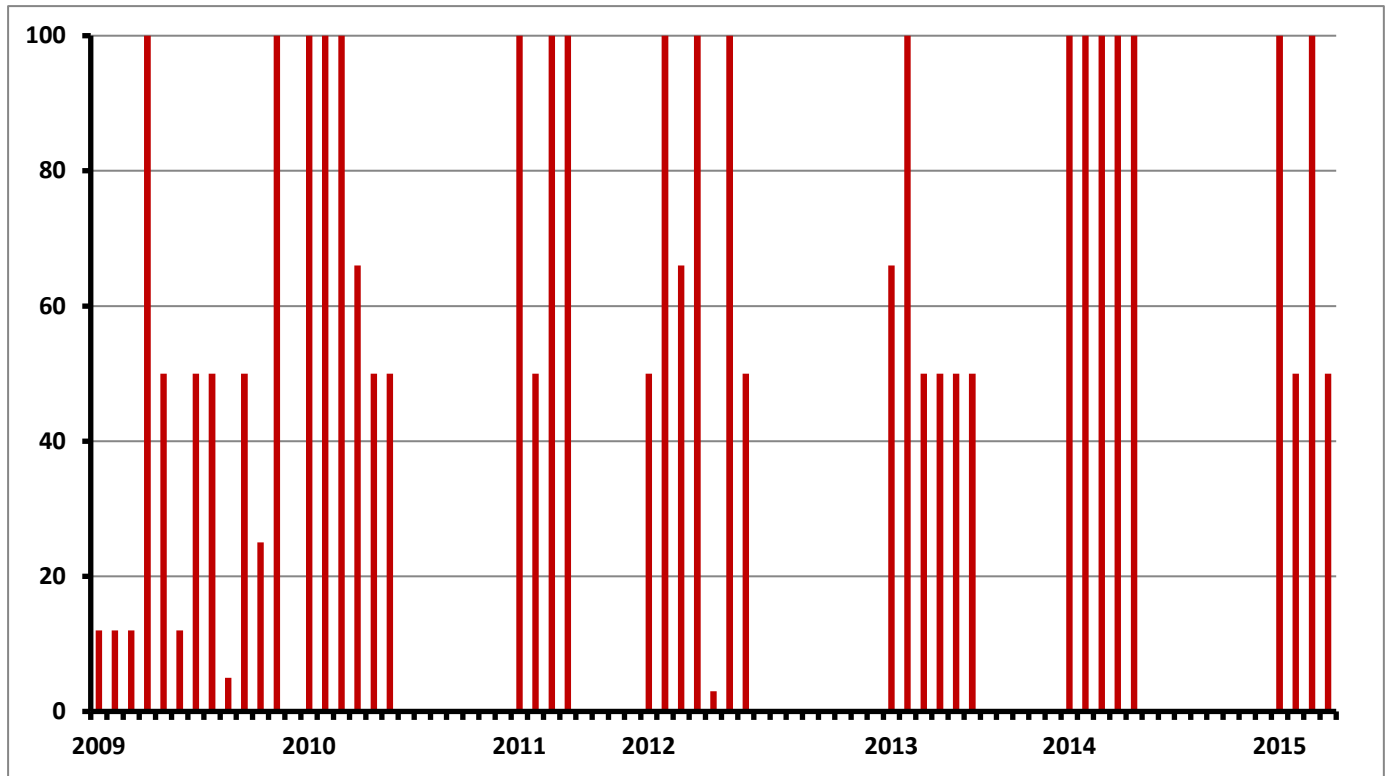


Figure 2C: Folic acid

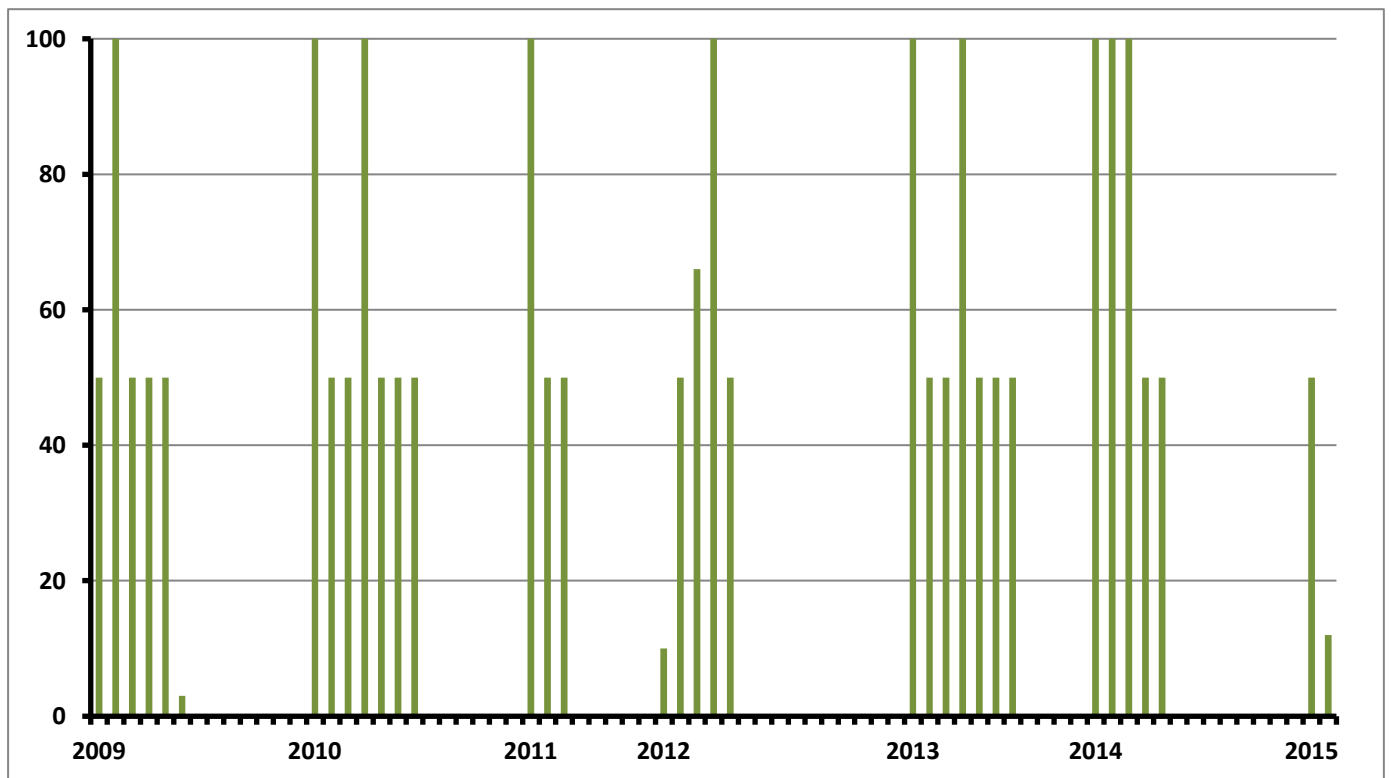


Figure 2D: PKU Cooler

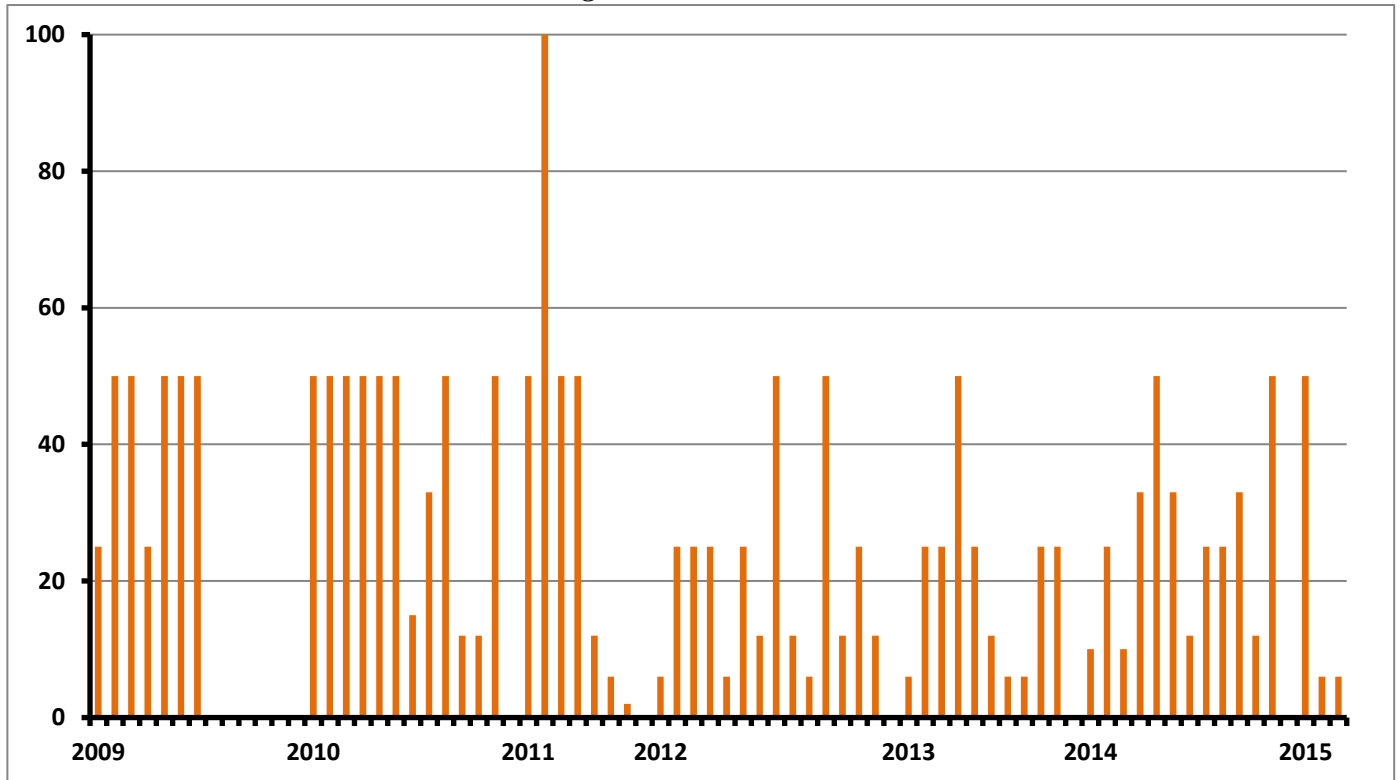
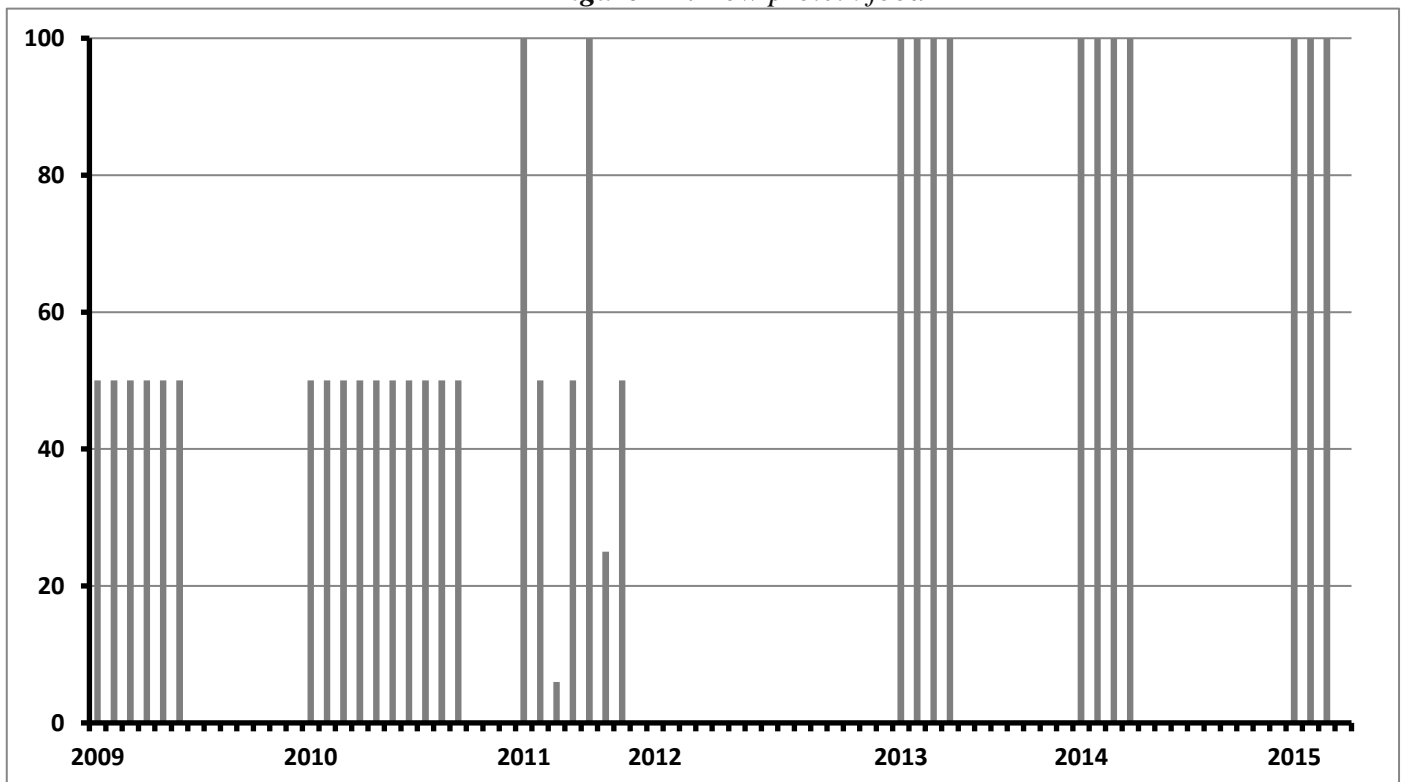


Figure 2E: Low protein food



**Legend to Figures 2A-E:** Prescriptions are denoted as a percentage of the amount ordered where 100% equals stock dispensed for a two month period. Amounts issued as a % of the totals ordered are shown for 5 items over 6.5 years, 2009-15. All items are frequently supplied in insufficient quantities: L-dopa 68%; 5HT 67%; low protein food (e.g. bread, pasta) 63%; folic acid 61%, and low protein drinks (PKU cooler) being the most affected, averaging just 30% of the requested stock being dispensed.

## Discussion

Phenylketonuria (PKU) in Malta is mostly due to dihydropteridine reductase (DHPR) deficiency, is not screened for at birth and presents late, invariably with developmental delay and neurodisability.<sup>5</sup> The management of this condition is complex and patients/their families face many challenges on a daily basis.<sup>5-8</sup> This study has shown that the burden of PKU in Malta is further compounded by non-adherence to PKU diets, in part, due to irregular provision of neurotransmitter and cofactor supplementation, as well as PKU-specific food items. Collectively, these children only consume small amounts of specific food items that change from time to time, and are not widely available, thereby discouraging local pharmaceutical agents to maintain stocks. Limited stocks lead to under-dispensing that, at best, is as much as 32% for some less problematic medications like L-dopa but may be as high as 70% of what is required for other items like low protein drinks (e.g. PKU Cooler). In practice, patients with PKU are issued with close-to-the-expected number of prescriptions per year with the exception of low protein drinks. For the latter, many more prescriptions are issued, presumably to 'make up' repeated deficits in the incomplete amounts dispensed. However, chronic under-dispensing was observed for all drugs and food items for PKU-related prescriptions, a situation that resulted in frequent hospital attendances to collect the shortfall. These extra hospital trips for repeat 'top-ups' are inconvenient but, more significantly, any delays in treatment are associated with increased symptoms as doses are missed and compliance with PKU-diet is suboptimal.

These shortfalls are the result of several factors including, at times, poor supply by the importing agents, compounded by the short half-life of some of these products especially the food products, milk and low protein drinks, and is not helped by the relatively costly and small quantities required. An inefficient procurement process with cumbersome tendering, little in-built flexibility and perpetual budgetary limitations often results in frequent 'out of stock' events, with subsequent incomplete/delayed prescriptions necessitating urgent and costly top-ups. In addition, food items frequently surpass their sell-by-date when collected by patients who, in turn, shun these items that are then discarded. Wastage begets ever more barriers

to future orders, incurs greater delays and creates a vicious cycle of negative supply.

Although this study is based on a qualitative review of a small number of patients, and carried out by the same patients' potentially biased caring physicians who may be equally frustrated with chronic under-dispensing for their patients, it nevertheless highlights a chronic problem for these patients and a significant lacuna in the service. This study would suggest that a comprehensive overhaul of the pharmaceutical provision for children with PKU with effective dietary and medicinal provision is essential. A serious exercise to address all of these issues is required, but one option whereby families are given a carefully monitored budget to procure and manage their own supplies is one model that can be applied for PKU and similar rare disorders that require multiple, 'special', hard-to-obtain, expensive items with a short half-life.<sup>9-10</sup> This would have to be combined with greater efficiency at the point of delivery by importing agents as it would otherwise simply transfer an added burden from the hospital pharmacy to the patient. In line with 'best practice', all these patients are managed in conjunction with a tertiary centre<sup>11</sup> and, alternatively, supplies could be obtained directly from the shared care tertiary centre in the UK, again with due monitoring from both health services. This set-up may also prove to be more cost-effective as it would eliminate wastage relating to expired/unused/surplus items. In tandem, a dedicated section/sub-department within the hospital service could be responsible for all aspects of supplies for PKU and related disorders, and would be expected to work closely with a local dedicated dietetic service that can closely monitor food items, 'sell by dates', stocks and supply, as well as liaise regularly with the tertiary metabolic centre.

## Conclusion

A small number of children with PKU require low phenylalanine food products with or without additional medications, and they should receive the required products at the right quantity and at the right time. Failure to do so results in neurological and behavioural symptoms in the short term and may compound neurodisability long term. This is an important issue that has ethical as well as potentially serious medico-legal implications. Despite strenuous efforts by all concerned, the

current system has repeatedly failed to provide adequate stocks, ensure in-date medications and avoid delays in the dispensing of PKU-related items. A comprehensive review of all aspects of the present set-up is required with urgency.

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