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Article

Compounded drugs as an alternative to the therapeutical gaps of inborn errors of metabolism

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Inborn errors of metabolism are rare disorders with few therapeutic options for their treatments, which can make patients suffer with complications. Therefore, compounded drugs might be a promising option given that they have the ability of meeting the patient's specific needs, (i) identification of the main drugs described in the literature; (ii) proposal of compounding systems and (iii) calculation of the budgetary addition for the inclusion of these drugs into the Brazilian Unified Health System. The research conducted a literature review and used management data as well as data obtained from official Federal District government websites. The study identified 31 drugs for the treatment of inborn errors of metabolism. Fifty eight percent (58%) (18) of the medicines had their current demand identified, which are currently unmet by the local Health System. The estimated budget for the production of compounded drugs was of R$363,16.98 per year for approximately 300 patients. This estimated cost represents a budgetary addition of only 0.17% from the total of expenditures planned for drug acquirement. There is a therapeutic gap for inborn errors of metabolism and compounding pharmacies show potential in ensuring access to medicine therapy with a low-cost investment.

Keywords: Rare diseases. Metabolism. Inborn errors. Therapeutic gap. Compounded drugs.

INTRODUCTION

Inborn Errors of Metabolism (IEM) are hereditary biochemical disorders where one can present metabolism abnormalities in a specific route due to deficit in enzymes, cofactors or enzymatic carriers (Camp, Lloyd-Puryear, Huntington, 2012). As a result, it is possible that an accumulation of the substrate in toxic levels occurs as well as a decrease of the enzymatic product (Camp, Lloyd-Puryear, Huntington, 2012; Gambello, Li, 2018).

The worldwide prevalence of IEM is of 50.9 cases per 100,000 live births and it is estimated that 70,000 new cases are diagnosed each year (Jardim, Ashton-Prolla, 1996). Newborns are usually asymptomatic, but around 25% of the patients with IEM have symptoms in early life stages (El-Hattab, 2015).

With more than 500 types of registered disorders, IEM mainly affect the pediatric population and represent about 10% of all genetic diseases. In Brazil, epidemiological data are limited, but it is estimated that this set of diseases can affect approximately 1/5000 live births. In the Federal District alone, approximately 500 consultations are carried out monthly to monitor patients with IEM (El husny, Caldato, 2006; Fachini, 2019).

The long path to getting the diagnosis and the delayed start to medicine therapy are directly linked to the occurrence of irreversible damage, specially in regards to the central nervous system (El-Hattab, 2015).

A difficult barrier that must be overcome for this group of diseases is the shortage of therapeutic

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options. Most of the recommended treatments have not even been used on randomized clinical trials in order to support their implementation in daily clinical practice, mainly because of the ethical issue concerning the performance of clinical trials with children. Moreover, there is not much of an economical interest of the pharmaceutical industry in investing in new therapeutic options (Schwartz, Souza, Giugliani, 2008). As a result, experts often lack consensus on the treatment that should be adopted for these patients (Schwartz, Souza, Giugliani, 2008; Alfadhel e*t al.*, 2013).

Progress has been made in studies regarding the molecular pathophysiology of IEM, which allowed some new approaches, such as the production of the deficient enzyme and its administration in the patient (Schwartz, Souza, Giugliani, 2008), the use of chaperone therapy to stimulate residual activity of the affected enzyme, gene therapy, cell therapy or even the use of conjugate therapies (Gambello, Li, 2018; Schwartz, Souza, Giugliani, 2008). Even though these alternatives seem promising, it might take a while until they get into the market with an accessible cost. Therefore, it is necessary to guarantee access to therapeutic alternatives already available for these patients.

The inclusion of therapeutic alternatives for the treatment of IEM in the public health system in Brazil bumps into the need to adapt formulas for use in pediatrics and for different types of metabolic disorders, which makes this challenge even more complex, highlighting the urgency of creating better treatment alternatives.

An available solution for this problem is the use of compounded drugs. These systems can be specific to each patient and meet their personal needs. A document from the Brazilian Ministry of Health even recommended that the Brazilian Unified Health System (SUS) use this strategy to guarantee access to pediatric formulas unavailable in Brazil (Brasil, 2018). Thus, compounding pharmacies show potential in promoting access to many therapeutic gaps of IEM, despite the lack of prognosis for their incorporation into SUS.

The present study aims to identify and describe potential pediatric presentations for the management of IEM, and to assess the budgetary increase of incorporating these systems into SUS.

METHODS

The research was conducted in three phases, which had the objective of: (i) defining the main drugs described in the literature for IEM (literature review); (ii) proposing compounding systems for the identified drugs and (iii) calculating the budgetary addition for including these drugs into SUS in a Brazilian state. The research was carried out with the use of aggregated information data, without the possibility of individual identification and, therefore, does not require submission to the CEP/CONEP system (Resolution MS 510/2016).

Identification of the main drugs indicated for the treatment of IEM

A literature review was performed using mainly review papers with consolidated or quasi-consolidated information on medicinal products with clinical use for the treatment of IEM diseases. From this data, a table containing the drugs found was constructed. The research for reviews was carried out in January of 2019 in the following databases: *Medical Literature Analysis and Retrieval System Online – MEDLINE/PubMed*, *SciELO – Scientific Electronic Library Online*, *Literatura Latino-Americana e do Caribe em Ciências da Saúde – LILACS* and *The Cochrane Library*. After the research, the papers were evaluated and the ones in accordance with the central theme of the study were explored.

For the research, we used operators and descriptors from the Medical Subject Headings – MeSH and from Descriptors in Health Sciences – DeCS, as well as their Portuguese, English and Spanish correspondent: ("Metabolism, Inborn Errors") AND ("diet therapy") AND/OR ("therapy") AND/OR ("drug therapy").

The inclusion criteria were studies that identified "nutraceuticals/medicines" for the treatment of IEM. Studies published over 10 years ago and those that did not address the topic were excluded. Studies that did not address pharmacological therapeutic alternatives were also excluded.

The assessment was done following, sequentially, (i) titles; (ii) abstracts and, finally, (iii) full texts. In addition,

some of the references of the selected articles were included. The obtained data were organized using the tool Excel®.

Proposal of a standard formula to compounded systems

After the data review on drugs used to treat IEM, we started to pursue the standard dosage for each drug on the databases *Dynamed*® and *Micromedex*®. This search included pediatric and adult standard dosages. The proposal was designed considering the standard dosages, prioritizing liquid systems given the prevalence of the pediatric population.

The feasibility of medicine production was evaluated through the search of compendiums on compounded drugs and based on the literature review. Additionally, we checked if any of the systems or any similar to them were registered on the Brazilian Drug Administration – National Health Surveillance Agency (ANVISA) and the availability of the formula compounds was evaluated on the national market through the "Brazilian Association of Distributors and Importers of Pharmaceutical Raw Materials" – *ABRIFAR* (Murray e*t al.*, 2012; Rowe, Shesekey, Quinn, 2012; Sweetman e*t al.*, 2009).

Rough budgetary addition for the inclusion of IEM drugs in the Federal District

The demand for treatment of IEM in the Federal District (DF) was accessed in collaboration with the Directorate of Pharmaceutical Services and the Coordination of Rare Diseases, both linked to the Secretariat of Health. This state was chosen because of the existence of specialized service, direct assistance by a single entity and the ability to raise the entire state demand. Based on the registered patients with a diagnosis of IEM, it was estimated the monthly demand of the proposed systems. It is important to highlight that currently these drugs are not formally made available by SUS and that access to them is made possible through private purchase, support from patient associations or specific local initiatives.

In regards to budget addition, the costs of each system were valued considering the direct, indirect, and operational costs for the production in a Compounded Public Pharmacy, and therefore, a profit percentage was not included on the balance. To assess the costs for active ingredients, the price quote in at least three distribution companies was obtained and the average between them was considered.

The direct costs of the system were the ones related to raw materials, packaging, and human resources. The indirect costs considered costs such as renting, personal protective equipment, quality control, waste collection, prevention of environmental risks, water supply, energy supply, maintenance, and cleaning material. Operational costs, on the other hand, are those that involved expenses related to monthly fees for information systems, telephone, internet, stationery supplies and accounting fees (Gambello, Li, 2018).

Considering the costs of each system and the monthly demand of all patients, an estimated annual addition to the Federal District budget was calculated.

RESULTS

Literature Review and Identification of the main drugs used to treat IEM

The search in 5 databases found 454 papers, of which only 16 were selected. Another 5 papers were included after a careful analysis of the references from the previously selected papers, bringing the literature review to a total of 21 papers (Figure 1).

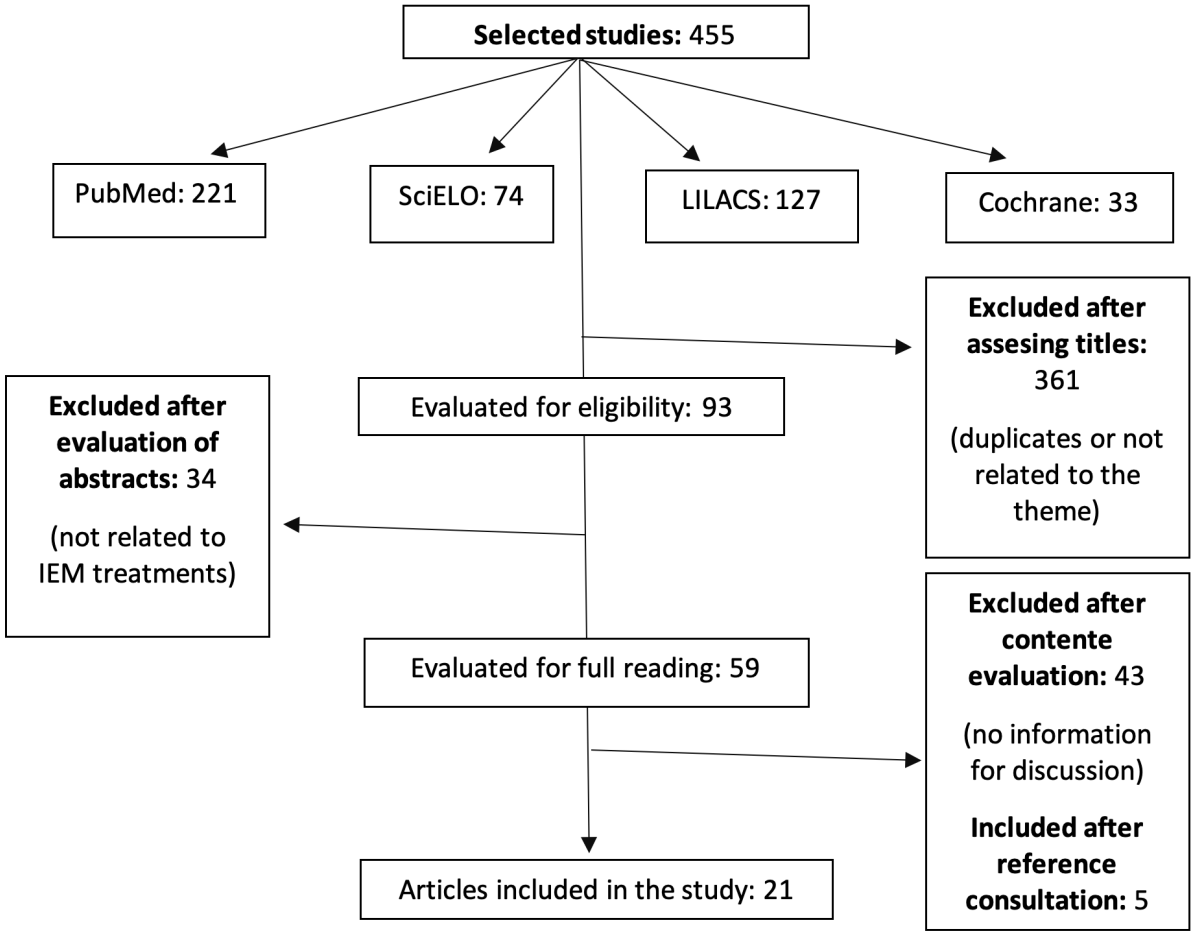

FIGURE 1 – Literature review process flowchart.

As shown in Table I, 31 active ingredients were found for the treatment of 12 different kinds of IEM. The number of available treatments for IEM indicates the need of an individual analysis of each patient, given that the medicine therapy may vary depending on the stage of the disease (Demirdas *et al*., 2013). This result points to a personalized solution that may be reached through the use of compounded medicines.

TABLE I – IEM and active ingredients/drugs used for their treatments

IEM	DRUG	REFERENCE
Organic Acidurias	Riboflavin	Alfadhel *et al.*, 2013 Lilliu, 2010
		Schwartz, Souza, Giugliani, 2008
	Sodium Benzoate	Baumgartner *et al.*, 2014
	Biotin	Lilliu, 2010
	Sodium phenylbutyrate	Häberle *et al.*, 2012 Lilliu, 2010
	Glycine	Alfadhel *et al.* 2013 Van Vliet et al., 2014
	Hydroxycobalamin	Baumgartner *et al.*, 2014
	L-Arginine	Häberle *et al.*, 2012 Van Vliet *et al.*, 2014
	L-Carnitine	Alfadhel *et al.*, 2013 Baumgartner *et al.*, 2014 Kölker *et al.*, 2011
	Lysine	Van Vliet *et al.*, 2014
	L-Isoleucine	Van Vliet *et al.*, 2014
	L-Valina	Van Vliet *et al.*, 2014
	N-carbamyl glutamate	Alfadhel *et al.*, 2013 Baumgartner *et al.*, 2014 Häberle *et al.*, 2012
	Thiamine	Lilliu, 2010
Pyridoxine-dependent Seizures	Pyridoxal Phosphate	Alfadhel *et al.*, 2013 Schwartz, Souza, Giugliani, 2008
Biotinidase deficiency	Biotine	Schwartz, Souza, Giugliani, 2008
Primary and Secondary Carnitine Deficiency	L-Carnitine	Lilliu, 2010
		Schwartz, Souza, Giugliani, 2008
		Sutton *et al.*, 2012
Glutathione Synthetase Deficiency	Vitamin E	Alfadhel *et al.*, 2013
Primary Coenzyme Q_{10} deficiency	Ubiquinone (Coenzyme Q_{10})	Alfadhel *et al.*, 2013 Schwartz, Souza, Giugliani, 2008

TABLE I – IEM and active ingredients/drugs used for their treatments

IEM	DRUG	REFERENCE
Urea cycle disorders	Sodium Benzoate	Häberle *et al*., 2012
		Lilliu, 2010
		Schwartz, Souza, Giugliani, 2008
	Biotin	Alfadhel *et al*., 2013 Baumgartner *et al*., 2014 Conitec, 2012
	Sodium phenylbutyrate	Schwartz, Souza, Giugliani, 2008
	L-Arginine	Häberle *et al*., 2012 Van Vliet *et al*., 2014
	L-Citrulline	Alfadhel *et al*., 2013 Häberle *et al*., 2012
	Lysine	Kölker *et al*., 2011
	N-carbamyl glutamate	Häberle *et al*., 2012 Schiff, Blom, 2012
	Pyridoxine	Schiff, Blom, 2012
	Pyridoxine	Schwartz, Souza, Giugliani, 2008
	Thiamine	Alfadhel *et al*., 2013 Frazier *et al*., 2014
Maple Syrup Urine Disease	L-Isoleucine	Alfadhel *et al*., 2013 Singh *et al*., 2016
	L-Valina	Alfadhel *et al*., 2013 Frazier *et al*., 2014
	Thiamine	Schwartz, Souza, Giugliani, 2008
Phenylketonuria	Glutamine	Van Vliet *et al*., 2014
	Sapropterina	Alfadhel *et al*., 2013 Cunningham *et al*., 2012 MacLeod and Ney, 2010 Singh *et al*., 2016 Somaraju, Merrin, 2015
Familial hypercholesterolemia	Atorvastatin	Vuorio *et al*., 2017
	Colesevelam	Davidson, 2011
	Colestipol	
	Cholestyramine	
	Pravastatin	O'Gorman *et al*., 2009 Vuorio *et al*., 2017
	Rosuvastatin	Vuorio *et al*., 2017
	Simvastatin	O'Gorman *et al*., 2009 Vuorio *et al*., 2017

TABLE I – IEM and active ingredients/drugs used for their treatments

IEM	DRUG	REFERENCE
Homocystinuria	Folic Acid	Alfadhel *et al*., 2013
	Betaine	Diekman *et al*., 2014 Morris *et al*., 2017
	Hydroxycobalamin	Schiff, Blom, 2012
	Pyridoxine	Morris *et al*., 2017
	Folinic Acid	Alfadhel *et al*., 2013 Schiff, Blom, 2012 Schwartz, Souza, Giugliani, 2008
Tyrosinemia Type 1	Phenylalanine	Van Vliet *et al*., 2014

Proposal of a standard compounded system

Table II presents the suggested doses of the drugs used for treating IEM, obtained from the literature review, as well as two databases (*Dynamed* e *Micromedex*).

TABLE II – Dosage identified for the drug list

ACTIVE INGREDIENT	DOSES		
	PAPERS	DYNAMED	MICROMEDEX
Folic Acid	5-30 mg/d	-	0,5-5mg/d
Folinic Acid	1-5 mg/d 5-15 mg/d 5-30 mg/d	-	-
Atorvastin	10-20 mg/d	10-20 mg/d	10-20 mg/d
Sodium Benzoate	150-250 mg/kg/d 200-300 mg/kg/d	-	-
Betain	150-250 mg/kg/d (in 2-3 doses) 5-20 g (in 2-3 doses)	-	100 mg/kg/d (2 doses)
Biotin	5-20 mg/d	1-10 mg/d	5-10 mg/d
Colesevelam	1,875 g or 3,75 g/d (2x) or (1x)	1,875 g or 3,75 g/d (2x) or (1x)	1,875 g or 3,75 g/d (2x) or (1x)
Colestipol	2-12 g/d	2 g/d (1-2x)	2 g/d (1-2x)
Cholestyramine	8 g/d	4 g (1 or 2x)	4 g (1 or 2x)
Phenylalanine	20-40 mg/kg/d	-	-
Sodium phenylbutyrate	500 mg/kg/d 200-600 mg/kg/d	-	450-600 mg/kg/d (in 3-6 doses)

TABLE II – Dosage identified for the drug list

ACTIVE INGREDIENT	DOSES		
	PAPERS	DYNAMED	MICROMEDEX
Glycine	150-300 mg (4 doses)	-	-
Glutamine	200-1000 mg/kg/d	-	-
Hydroxycobalamin	5-21 mg/week 1 mg/day or 1 mg/week	-	400 mcg/d
L-Arginine	100-300 mg/kg/d	-	-
L-Carnitine	100-300 mg/kg/d (in 2-4 doses)	50-100 mg/kg/d (in 2-3 doses)	50 mg/kg/d (divided doses)
L-Citrulline	100-200 mg/kg/d	-	-
Lysine	50-100 mg/kg/d	-	-
L-Isoleucine	20-120 mg/kg/d	-	-
L-Valina	20-120 mg/kg/d	-	-
N-Carbamyl Glutamate	100-250 mg/kg/d (in 3-4 doses)	100-250 mg/kg/d (in 2-4 doses)	100-250 mg/kg/d (in 2-4 doses)
Pyridoxal Phosphate	30-50 mg/kg/d (in 4-6 doses)	-	-
Pyridoxine	10 mg/kg/d-500 mg/d$^{(max)}$	-	-
Pravastatin	5, 10, 20 ou 40 mg/d	40 mg/d	20 ou 40 ou 80 mg/d
Riboflavin	100-150 mg/d (in 2-3 doses)	-	-
Rosuvastatin	5-20 mg/d	5-20 mg/d	20 mg/d
Sapropterina	5-20 mg/kg/d	10 mg/kg/d	10 mg/kg/d
Simvastatin	10-40 mg/d 20 mg/d	10-40 mg/d	5-40 mg/d
Thiamine	10-1000 mg/d	-	-
Ubiquinone (Coenzyme Q_{10})	2-15mg/kg/d (2x/day)	-	-
Vitamin E	10 mg/kg/d	-	-

When evaluating the obtained data, it is possible to identify a wide range of treatments for the studied diseases, as there is no consensus or standard dose suggested for the treatment of each illness. It happens due to the particularities of the affected patients, since those metabolic diseases might present themselves in different ways for each individual considering the adaptive biochemical process (Wagner, 2007).

On the other hand, there is agreement in regard to dosage between distinct sources, demonstrating that data could be taken as a basis for the definition of standard systems, which allow dose adjustment with relative safety. In this sense, liquid presentations can be suggested as an alternative to fill this gap.

The review allowed the identification of 31 drugs that are part of a main list for the management of IEM. Medicines

that included enzymes or biologic products were excluded from the study due to the impossibility of producing them in compounding pharmacies.

In Table III, the proposed dose was defined through a standard dosage based on the prescription showed in Table II.

TABLE III – Proposed list of products to be developed as compounded drugs for the treatment of IEM

N°	DRUG	STANDARD DOSAGE	PHARMACEUTICAL PRODUCT TO BE DEVELOPED FOR CHILDREN
1	Folic Acid	5mg/d	Oral solution 5mg/mL (30mL)
2	Folinic Acid	10mg/d	Oral solution 10mg/mL (100mL)
3	Atorvastin	10mg/d	Oral solution 10mg/mL (100mL)
4	Sodium Benzoate	200mg/kg/d	Oral solution 250mg/mL (100mL)
5	Betain	100mg/kg/d (in 2 doses)	Oral solution 250mg/mL (120mL)
6	Biotin	10mg/d	Solution 10mg/mL (60mL)
7	Colesevelam	1,875g/d (2x/d)	Oral solution 1,875g/mL (60mL)
8	Colestipol	2g/d (1-2x/d)	Oral solution 2g/mL (60mL)
9	Cholestyramine	4g/d (1-2x/d)	Oral solution 4g/mL (60mL)
10	Phenylalanine	20mg/kg/d	Oral solution 100mg/mL (100mL ou 200mL)
11	Sodium phenylbutyrate	450mg/kg/d (in 3-6 doses)	Oral solution 450mg/mL (150mL)
12	Glycine	200mg/kg/d (in 4 doses)	Solution 250mg/mL (120mL)
13	Glutamine	200mg/kg/d	Oral solution 250mg/mL (100mL)
14	Hydroxycobalamin	400mcg/d	Oral solution 400mcg/mL (30 mL)
15	L-Arginine	100mg/kg/d	Solution 500mg/mL (100mL)
16	L-Carnitine	100mg/kg/d (in 2-4 doses)	Oral solution 125mg/mL (100mL)
17	L-Citrulline	100mg/kg/d	Solution 500mg/mL (100mL)
18	Lysine	50mg/kg/d	Oral solution 250mg/mL (100mL)
19	L-Isoleucine	50mg/kg/d	Solution 250mg/mL (100mL)
20	L-Valina	50mg/kg/d	Oral solution 250mg/mL (100mL)
21	N-Carbamyl Glutamate	100mg/kg/d (em 2-4 doses)	Solution 125mg/mL (120mL)
22	Pyridoxal Phosphate	40mg/kg/d (in 4-6 doses)	Oral solution 50mg/mL (120mL)
23	Pyridoxine	10mg/kg/d	Oral solution 50mg/mL (100mL)

TABLE III – Proposed list of products to be developed as compounded drugs for the treatment of IEM

N°	DRUG	STANDARD DOSAGE	PHARMACEUTICAL PRODUCT TO BE DEVELOPED FOR CHILDREN
24	Pravastatin	10mg/d	Oral solution 10mg/mL (100mL)
25	Riboflavin	200mg/d (in 2-3 doses)	Solution 100mg/mL (100mL)
26	Rosuvastatin	20mg/d	Oral solution 20mg/mL (100mL)
27	Sapropterina	10mg/kg/d	Oral solution 50mg/mL (100mL)
28	Simvastatin	20mg/d	Oral solution 20mg/mL (30mL)
29	Thiamine	200mg/d	Oral solution 200mg/mL (120mL)
30	Ubiquinone (Coenzyme Q_{10})	5mg/kg/d (2x/d)	Oral solution 25mg/mL (100mL)
31	Vitamin E	10mg/kg/d	Oral solution 50mg/mL (100mL)

The proposed pharmaceutical system considered the age group it would be administrated to. That way, there was a preference for pharmaceutical oral liquids (solution or suspensions) for pediatric products and oral solids for adults.

To define the oral liquid systems, the weight range of the user was defined as between 5kg and 50kg, considering data from the Brazilian Institute of Geography and Statistics (IBGE). Therefore, the range of dosage for these systems might go from 1 to 10 mL, which are reasonable and common for industrialized products.

The development of pharmaceutical systems must include a systematic evaluation of physicochemical aspects related to active ingredients and excipients, as well as methods for quantifying active ingredients, considering quality control and stability determination of these products, which will be further developed for this group in advanced stages of the research. However, the list proposed in Table III aims to provide initial information for planning this development, being useful as a starting point for defining the feasibility of producing these medicines.

Inclusion of IEM medicines in SUS and their addition to the Federal District budget

The list of medicines found for treating IEM was compared to the demand of drugs for treating these diseases on patients assisted by the Genetics Services of the Brasília Support Hospital of the Federal District. From the 31 drugs identified in this study, 18 (58%) had been requested to the Health Secretariat, in the exact presentations proposed or with small variations. This demand was accessed through the prescriptions for IEM patients within a year.

Besides these 18 drugs, other 4 drugs, which were not included in the first phase of the study, were described: alanine, hydrocortisone, L-tyrosine, and fludrocortisone. Those drugs were not described in any paper selected and no information was found regarding dosage for the treatment of IEM, which hindered the proposal of a compounded system for them straightaway.

The pharmaceutical presentations with proved demand in the Federal District are described in Table IV.

TABLE IV – Qualitative and quantitative demand for medicines for IEM in the Federal District

Nº	DRUG	ESTIMATED MONTHLY PRESCRIPTIONS (N°)	ESTIMATED MONTHLY COST (BRL$)	ESTIMATED ANNUAL COST (BRL$)
1	Folic Acid oral solution 5mg/mL (30mL)	20	976.14	11,713.68
2	Folinic Acid oral solution 10mg/mL (100mL)	05	661.35	7,936.20
3	Sodium benzoate oral solution 250mg/mL (100mL)	30	2,941.20	35,294.40
4	Betaine oral solution 250mg/mL (120mL)	10	1,547.00	18,564.00
5	Biotin solution 10mg/mL (60mL)	30	1,568.25	18,819.00
6	Glycine solution 250mg/mL (120mL)	10	814.45	9,773.40
7	Glutamine oral solution 250mg/mL (100mL)	10	839.20	10,070.40
8	Hydroxycobalamin oral solution 400mcg/mL (30 mL)	50	3,888.00	46,656.00
9	L-arginine solution 500mg/mL (100mL)	15	1,255.50	15,066.00
10	L-carnitine oral solution 125mg/mL (100mL)	50	4,361.00	52,332.00
11	L-isoleucine solution 250mg/mL (100mL)	05	418.50	5,022.00
12	L-valine oral solution 250mg/mL (100mL)	05	412.13	4,945.50
13	Pyridoxal phosphate oral solution 50mg/mL (120mL)	10	1,244.50	14,934.00
14	Pyridoxine oral solution 50mg/mL (100mL)	30	2,815.50	33,786.00
15	Riboflavin solution 100mg/mL (100mL)	30	2,596.50	31,158.00
16	Thiamine solution 200mg/mL (120mL)	30	2,911.80	34,941.60
17	Ubiquinone (Coenzyme Q_{10}) oral solution 25mg/mL (100mL)	10	616.20	7,394.40
18	Vitamin E oral solution 50mg/mL (100mL)	10	459.20	5,510.40
TOTAL		**360**	**BRL$ 30.326,42**	**BRL$ 363.916,98**

From the demand presented in Table IV, it is possible to suggest a monthly estimative of prescriptions that would result in the production of 360 drugs units. This number tends to increase, given the possibility of new diagnoses and that the dosage could be adjusted for the same patient during treatment.

DISCUSSION

Pediatric patients affected by IEM are a heterogenic group in terms of the variety of rare diseases that comprise it. An important highlight is that, when analyzed as a group, IEM have a prevalence of 500 cases per a million

of live births, with a child mortality of 3.2 deaths per each 100.000 live births worldwide (Waters *et al.*, 2018)**.** This implies a really low demand, which justifies the market's lack of interest in the diagnosis, treatment and prevention of these conditions. However, IEM represent an important public health issue, given that the affected population is composed by newborns and children who may present severe neurological sequelae due the absence of treatments for their specific condition.

The literature review shows specific results for the diseases that are part of this group, such as: phenylketonuria, maple syrup disease, familial hypercholesterolemia, organic aciduria, homocystinuria, and urea cycle disorders. These results demonstrate that among different groups within IEM, the particularities of each disease require specific therapeutic approaches.

For pediatric patients or people with rare diseases, the option of having personalized treatment at compounding pharmacies might collaborate with the treatment because it allows access to medicine therapy, dosage adjustment, replacement of undesirable formulation components, manipulation of associations to improve adherence or to reduce errors.

The need of beginning this study with an exhaustive literature review aimed to demonstrate therapies with higher evidence level in order to help clinical decisions and identify interventions with confirmed efficacy (Pailaquilén, Medina, 2010). The lack of studies for IEM prevents higher evidence levels to be reached and this precludes the evaluation of efficacy on existing treatments. Moreover, this exposes the problem of lack of consensus for drug dosages, given that there are many variations when more than one source is analyzed (Alfadhel *et al.*, 2013; Wilcken, 2001).

For this study, the chosen pharmaceutical system took into consideration the one that would be more convenient for children, since they are the main group affected by IEM. It is known that oral solutions and suspensions are of easy dose adjustment. Likewise, they have the benefit of being easy to swallow and the possibility of organoleptic changes (Costa, Lima, Coelho, 2009).

None of the drugs identified on this study were registered as liquid systems in Brazil even when searched for in different concentrations. It is known that there is a lack of liquid pharmaceutical systems for prevalent diseases, and this lack is even worst for rare conditions.

Local well-structured actions are already demonstrating the ability of compounding medicines to fill therapeutical gaps in SUS, both at the hospital and at the outpatient level. Pereira *et al* (2016) identified the need to adapt, in a pediatric hospital, almost 657 medicines for use in neonatology, which represents 70% of the total. The possibility of producing these pharmaceutical systems prevented common handling errors when they are performed in nursing stations, such as the use of an inappropriate vehicle or incorrect packaging and conservation, which may occur in 75.6% of cases (Costa, Lima, Coelho, 2009; Pereira *et al.*, 2016).

In another service connected to a compounding pharmacy of the health department, Borrella and Pereira (2017) showed that besides the large production capacity of a public pharmacy (34 thousand units in 2015), the unit cost of production for the state was between 186%-802% lower than the potential purchase from private pharmacies (Borella, Pereira, 2017).

This study presented a brief estimate of the annual budgetary addition for handling the current demand of treatment of IEM patients in DF. It is considered as minimum, for each item, the dispensation of at least one flask per month for each patient. The monthly budgetary increase found was of R$ 363.916,98. This amount is feasible given the scope of health problems that would be solved, and in comparison with the total budget foreseen for the purchase of medicines in the Federal District. Moreover, it is a much lower number than the budgetary addition for incorporating much more expensive health technologies that have already been approved by the National Committee for the Incorporation of Technologies in the Unified Health System (CONITEC), which will be discussed below. When compared to the annual budget foreseen for the acquisition of all medicines in DF in 2019, the value found represents only 0.17% of the total (R$211,055,238.00), which is a very low addition to the budget and reinforces that the investment to include these products at local health services would be an excellent investment.

In a national level, this impact might be even lower, especially when compared to recent IEM drugs incorporated by CONITEC, such as: Sapropterin, Alfaelosulfase, Galsulfase, Laronidase and Idursulfase Alpha, which are indicated for Phenylketonuria and Mucopolysaccharidoses IV, VI, II, and I respectively. The information on the recommendation reports from CONITEC for each of these medications showed that these technologies were approved based on budgetary impact for the first year of implementation, which considered the estimated number of patient users, the average number of ampoules or pills for each patient and the cost of each ampoule or pill (CONITEC, 2018a; 2018b; 2018c; 2017a; 2017b). The budgetary impact and the estimated number of users of the aforementioned drugs can be described as follows: (i) Idursulfase with 247 patients and an impact of 208 million; (ii) Galsulfase with 183 patients and an impact of 255 million; (iii) Laronidase with 105 patients and an impact of 44 million; (iv) Alfaelosulfase with 95 patients and an impact of 156 million; (v) Sapropterin with 580 responsive patients and an incremental impact to the existing treatment of 79 million (CONITEC, 2018a; 2018b; 2018c; 2017a; 2017b).

CONCLUSION

In an initial observation, taking into account just the budgetary addition and the estimated demand of CONITEC to IEM, it is highlighted the feasibility of incorporating compounded drugs for the treatment of IEM disorders in SUS. In fact, around R$400.000 would be enough to reach the demand of an entire year in a reference hospital for treatment of rare diseases in Federal District, initially benefiting more than 300 patients.

The inclusion of a service of compounding production of medicines by SUS becomes a promising strategy to help meet the unattended demands for rare and neglected diseases.

Future research should address issues of the development of the compounded systems in order to guarantee adequate characteristics of quality, effectiveness, and stability. Furthermore, studies should address effectiveness and adverse events analysis of the compounded systems after it has been administered in the patients, in pursuance of monitoring their use and contributing with pharmacovigilance data.

Thus, a strategy used to solve the problem at a local level has the potential to be expanded nationally and even internationally, taking into account the insufficiency of therapeutic alternatives found in the scientific articles that were used to develop the review.

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