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Barriers to drug adherence in the treatment of urea cycle disorders: Assessment of patient, caregiver and provider perspectives

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ABSTRACT

Patients and families living with metabolic disorders face challenging dietary and drug treatment regimens. On the hypothesis that poor palatability, volume and frequency of drug/formula administration contribute to treatment non-adherence and hyperammonemic episodes, a survey was conducted of patient, caregiver (CG) and physician perspectives on treatments used in urea cycle disorders (UCD).

Methods: A paper and online survey assessed experience with UCD medications, medical foods and dietary supplements.

Results: 25 physicians, 52 adult patients and 114 CG responded. In 2009, the most common UCD-specific intervention reported by patients included sodium phenylbutyrate (60%), followed by L-citrulline (46%), amino acid medical foods (15%), L-arginine preparations (18%), and sodium benzoate (8%). Only 36% of patients reported experiencing no hyperammonemic episodes in the last 2 years. The most commonly reported cause of hyperammonemic episodes was infection or other acute illnesses, followed by dietary indiscretion, side effects of medications, and drug non-adherence. Most patients, caregivers and physicians (>75%) ranked nitrogen-scavenging medications, L-citrulline, L-arginine, and medical foods as "effective" or "very effective." Non-adherence was common (e.g. 18% of patients admitted to missing sodium phenylbutyrate "at least once a week" and "at least one a day"). Barriers to adherence included taste of medications, frequency of drug administration, number of pills, difficulty swallowing pills, side effects, forgetting to take medications, and high cost. Strategies to mitigate the gastrointestinal side effects of medications included the use of gastric tubes and acid reflux medications. Physicians indicated that 25% and 33% of pediatric and adult patients, respectively, were given less than the recommended dose of sodium phenylbutyrate due to concerns of tolerance, administration, and cost.

Conclusions: Despite positive views of their effectiveness, respondents found medications, medical foods and dietary supplements difficult to take and viewed adherence as inadequate, thus contributing to hyperammonemic episodes.

1. Introduction

Urea cycle disorders (UCDs) represent a group of inborn errors of metabolism involving enzymes or transporters essential for the normal hepatic function of the urea cycle, which mediates removal of waste nitrogen through formation of urea excreted in the urine. UCDs are associated with episodic hyperammonemic crises (HACs) and a high risk of disability and mortality. The mortality rates with neonatal-onset and later-onset UCDs are approximately 24% and 11%, respectively [1,2]. The overall prevalence of UCDs is ~1:35,000 suggesting that 110–120 newborns affected by these disorders are born annually in the US [1,2].

Like many other metabolic disorders such as phenylketonuria, UCDs are managed through a combination of dietary restrictions, medical foods, supplements and drug therapy. Control of blood ammonia and prevention of HACs are key objectives of disease management, which typically includes restriction (often severe) of dietary protein, use of

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dietary supplements including urea cycle intermediates (e.g. arginine, citrulline) and medical foods (e.g. essential amino acids) and, when dietary measures and supplements are insufficient, nitrogen scavengers such as sodium phenylbutyrate (NaPBA) or sodium benzoate (NaBZ). Factors triggering hyperammonemia are complex and include infections, medications and diet events, major life events, pregnancy and menses [2–5]. These factors can contribute to hyperammonemic episodes in isolation (e.g., recent prescription changes, or improperly followed recipe to prepare formula) or through a more complex interaction (e.g., gastrointestinal infection preventing drug and medical foods administration). It has been estimated that 20–25% of acute HACs in UCD patients may be related to compliance issues with medications or diet [3,4].

In chronic non-genetic disorders, non-adherence to prescribed medications is a recognized barrier to achieving optimal treatment outcomes [6]. It is estimated that up to ~70% of hospital admissions in the general population are related to poor medication adherence costing the US economy >$100 billion a year [6–8]. Side effects, complexity of treatment, dose frequency, and cost of medications have all been identified as predictors of poor adherence to medications in context of chronic non-genetic conditions [6]. Considerably fewer studies have been devoted to non-adherence in metabolic disorders. For example, in phenylketonuria, poor palatability of amino acid formulas and burden of diet is often cited as barriers to optimal dietary adherence [9,10]. However, unlike in patients with phenylketonuria, where the clinical consequences of dietary non-adherence are insidious in nature, failure to adhere in urea cycle disorders may precipitate a serious hyperammonemic event [3,11].

To date, the magnitude and specific components of medical treatment contributing to non-adherence in the UCD community have not been systematically evaluated. This study represents a descriptive baseline assessment of adherence behaviors and mitigation strategies to inform our future interventions.

2. Methods

The survey was designed by Harris Interactive, Inc. (New York, NY) with input from the National Urea Cycle Disorder Foundation (NUCDF) (www.NUCDF.org) and conducted in the second half of 2008. The analyses were completed in the first half of 2009. Its purpose was to assess current attitudes of patients with UCDs and their CG and providers toward current treatment options, including dietary supplements, medical foods and formulas and nitrogen-scavenging medications. CG were included, as many UCD patients are children and/or are sufficiently disabled as to require the assistance of CG, many but not all of whom are parents.

The National Urea Cycle Disorders Foundation (www.NUCDF.org) provided project oversight for the study and collaborated with Harris Interactive to develop survey questions, provide confidential (redacted) contact information and perform mailings of surveys to families to maintain confidentiality of the study participants. A central institutional review board (IRB), Quorum IRB (Seattle, WA) was consulted to review the survey study for assessment of exemption of IRB review, which was granted.

Patients and CG received mail invitations to complete either an online or paper survey. Physician investigators in the NIH-funded Urea Cycle Disorders Consortium (http://www.rarediseasesnetwork.org/ucdc/index.htm) and all users in the Wolters-Kluwer database who had written ≥20 prescriptions for sodium phenylbutyrate (NaPBA) tablets or ≥36 prescriptions for NaPBA powder in the last 2 years were invited to participate. Only physicians who had treated at least one UCD patient and had been in practice for ≥2 years were included. Patients included in the study needed to be ≥18 years of age, diagnosed with a UCD and caregivers (CG) needed to have cared for someone diagnosed with a UCD within the past 5 years. Nominal honoraria ($20 gift card for patients/CG; $75 for physicians) were offered for survey participants.

Survey weighting was used as a quantitative approach to allow survey data to be representative of the target population, thereby allowing for differences in the numbers of certain subgroups surveyed. Harris Interactive statisticians and methodologists developed a data weighting approach to help ensure that results from this survey accurately represented the populations of UCD patients as well as their CG and physicians. The patient/CG data in this study were weighted based on the number of people with UCD in a specific household so that the data generated from each household would be proportionate to the number of people living in the household who were diagnosed with UCD.

3. Results

3.1. Patient and caregiver demographics and care utilizations patterns

Of 593 invited patients, CG and physicians, 191 (31% of patients/GC and 33% of physicians) responded, qualified and completed the survey, including 52 patients and 114 current/past CG (Table 1) and 25 providers (Table 2). Overall, ~33% of respondents were UCD patients (including 11% of current CG). Most (88%) CGs were parents of an affected individual and were very familiar with the care of patients with UCDs. Typical CG tasks included attending doctor's appointments (91%), managing diet (87%), administering medications (85%), purchasing medications (81%) and reminding the patient to take a medication (51%).

The most common UCD-specific medical interventions as reported by patients included NaPBA (60%). NaPBA was followed in frequency by L-citrulline (46%), amino acid medical formulas (15%), L-arginine free base (10%), sodium benzoate (NaBz) (8%), L-arginine HCl solution (8%), caloric supplements including Polycose (7%), Duocal (2%), L-carnitine (8%) as well as other non UCD specific medications including Adderall XR, Abilify, Wellbutrin (3% each). CG provided similar responses to frequency of medical interventions for UCD patients they care for: NaPBA (57%), amino acid medical foods (56%), L-citrulline (51%), L-arginine free base (26%), and NaBz (17%), among others. Of note, 30% of CG reported their patients use Prophree for UCD. Among respondents who have ever taken NaBP, 50% indicated that they or the person they cared for had a G-tube or an NG-tube. In 14%, caregivers

Table 1
UCD survey patient/caregiver demographics.

All respondents (N = 166)[a]	Summary statistic
Female	86%
Mean (SD) age in years[c]	41.0 (12.5)
18–24 years	9%
25–39 years	43%
40–59 years	32%
>60 years	8%
Diagnosed with UCD[c]	33%
Patients only (n = 52)[c]	
Mean (SD) patients' age at diagnosis, years	19.4 (14.5)
Mean (SD) number of UCD patients in household	1.3 (1.5)
Primary caregiver of a UCD patient	34%
Current/past caregiver (n = 114)[b]	
Mean (SD) number of patients cared for	1.2 (0.5)
Mean (SD) age at diagnosis in years	2.2 (3.2)
Mean (SD) years since diagnosis	10.2 (9.2)
Relationship to patient:	
Parent	88%
Grandparent	4%
Sibling	1%
Spouse	1%
Other family member	5%
Professional caregiver	1%
Other	2%

[a] The total sample size is derived from 52 patients, 90 current caregivers, and 14 past caregivers.
[b] Data presented includes patients responding to the survey who are also caregivers (n = 10) plus current (n = 90) and past (n = 14) caregivers.
[c] Male and female patients.