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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.

Table 2
Participating physician demographics.

	Total physicians (N = 25)
Female	28%
Mean age (SD) in years	52.0 (9.5)
Board certified or board eligible specialties*	
Endocrinologist	12%
Internal medicine	4%
Medical/clinical genetics	60%
Medical/clinical biochemical genetics	72%
Neurology	4%
Pediatrics	76%
Other	8%
Mean years of practice (SD)	18.6 (10.3)

Number of UCD patients followed by age	Patients per physician Mean (SD)	Total patients N
0–12 months	1.3 (1.5)	33
13–23 months	1.0 (1.6)	25
2–5 years	2.8 (3.3)	69
6–17 years	4.0 (3.4)	101
>18 years	4.9 (4.2)	122
Total	14.0	350

* A physician can be board-certified in more than one specialty.

indicated that tube placement had been performed solely to facilitate drug administration, whereas in 71% it was performed to help with administration of both food/formula and drug.

3.2. Patient reported frequency and causes of hyperammonemic crises

Thirty-six percent of patients reported no HACs in the last 2 years, with smaller percentages reporting "1–5 episodes" (25%), "6–10 episodes" (6%), and ">10 episodes" (26%). The median number of reported episodes was one or two. Regarding hyperammonemic episodes experienced in the last year, patients reported that the mean number of episodes of HAC related to viral infections and other acute illnesses was 2.7, dietary indiscretion was 2.6, side effects of medications was 1.3, and non-adherence to medications was 0.9.

3.3. Healthcare provider demographics and prescribing practices

Seventy-five US providers were invited to participate; 25 qualified and completed the survey (32% response rate; Table 2). The mean length of time in clinical practice since completing their residency/fellowship training was 18.6 years, including "1–10 years" in 28%, "11–20 years" in 40%, "21–30 years" in 20% and "31–40 years" in 12%.

3.4. Reported efficacy and safety and patient compliance

Eighty-six percent of patients and 88% of CG reported that NaPBA is either effective or very effective in controlling UCD symptoms (Fig. 1). NaBz was reported as effective and very effective by 80% of patients and 79% of CG who had experience with the medication. Among physician respondents, NaPBA was reported as the most effective available drug at controlling UCD symptoms by all physicians and NaBZ was regarded as "very effective" or "effective" by 93%. NaPBA was reported as "very safe" or "safe" by 92% of prescribers and NaBZ by 86%. However, physicians expressed concerns ("very concerned" and "concerned") about the side effects of NaPBA (46%) and NaBZ (36%).

Most physicians reported concerns about the difficulty of medication administration (NaPBA 83%, NaBZ 79%). Physicians indicated that 58% of patients taking NaPBA and 64% of patients taking NaBZ were compliant or very compliant with the prescribed medication. Other medication modalities showed high rates of adherence: 95% of prescribers reported that their patients were "very compliant" or "compliant" with L-citrulline, 84% with L-arginine free base, 88% with L-arginine hydrochloride, and 71% of physicians thought that their patients were

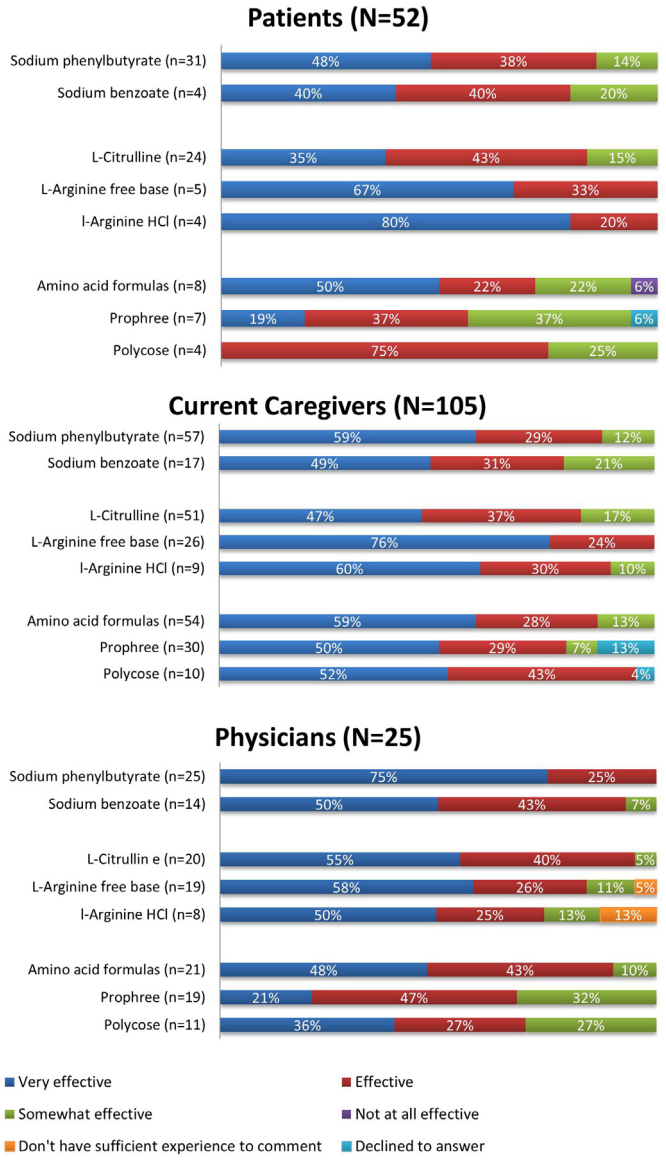

Fig. 1. Reported efficacy of medical interventions. The figure depicts the number of patients, current caregiver and physician respondents and percentage of respondents in each category that reported UCD drugs and dietary supplements falling into one of several categories, including highly effective, effective, somewhat effective, not at all effective, or insufficient experience. "N" represents the total number of respondents who answered at least one question. "n" represent number of respondents with experience with medication. Weighted base was used to calculate percentages.

"very compliant" or "compliant" with prescribed amino acid formulas. Table 3 summarizes reasons for medication and supplement non-adherence.

3.5. Dosage, safety, and adherence to ammonia scavengers

3.5.1. Sodium phenylbutyrate

NaPBA was taken by patients most commonly every 8 (17%) or 6 (27%) hours, with 11% taking it in powder form versus 89% taking it as pill. Eighty-percent of patients reported "some" or "a lot" of side effects from NaPBA. The frequency of side effects was similar across formulation (powder vs. pills) or dosing frequency. Regarding specific NaBPA adverse reactions, among patients who had ever taken NaPBA, ~20–30% of patients/CG reported gastrointestinal side effects as occurring "often" or "almost always", including nausea or vomiting, stomach/gastric distress, and decreased appetite. Patients (64%) reported that NaPBA is difficult to take because of its taste and strong odor. CG also

Table 3
Physicians' characterization of reasons for non-adherence with UCD treatment.

	NaPBA	NaBz	L-Citrulline	L-Arginine free base	Arginine hydrochloride (10% solution)	Amino acid formulas	Prophree	Polycose
The amount of medication taken each time	90%	50%	25%	31%	40%	39%	46%	50%
Difficulty in swallowing medication	81%	50%	17%	31%	40%	39%	8%	–
The number of times medication is taken each day	71%	64%	50%	54%	40%	33%	23%	17%
Patients forget to take it	71%	71%	75%	62%	60%	17%	38%	33%
Side effects from the medication	67%	36%	17%	23%	40%	11%	15%	–
Difficulty keeping the medication down	62%	36%	–	23%	40%	6%	–	–
Other	19%[a]	7%	17%[b]	23%[c]	20%[d]	28%[e]	23%[f]	17%

Abbreviations: NaPBA – sodium phenylbutyrate; NaBz – sodium benzoate.
[a] Taste, odor, expense.
[b] Taste and expense.
[c] Taste and texture.
[d] Difficult to digest.
[e] Taste and odor.
[f] Taste and "no reason" given.

reported body odor (45%) and burning sensation in mouth or throat (23%). Forty-two percent of physicians reported gastric distress as "common" or "very common" adverse reaction to NaPBA. When NaPBA was stopped, among the reasons leading to discontinuation, patients/CG mentioned its taste (47% of patients), "doctor recommending another treatment" (20%), liver transplant (20%), number of pills or amount of powder (17%), side effects (17%), and high cost (10%). Coping strategies reported by patients for mitigating NaPBA gastrointestinal side effects included H_2-blockers (7–52%), proton pump inhibitors (15–33%) and calcium carbonate (63%).

When physicians were asked about the reasons for daily non-adherence with NaPBA, those most commonly mentioned included "the amount of medication taken each time" (90%), "difficulty in swallowing the medication" (81%), "patients forget to take it" (71%), the dosing frequency (71%), side effects (67%) or "difficulty keeping the medication down" (62%). When asked about their patients, only 13% of physicians regarded their patients to be "very compliant" with the recommended therapy. In contrast, 58% of CG and 25% of patients, respectively, indicated they never miss NaPBA. Eighteen percent of patients admitted to missing the medication "at least once a week" and "at least one a day." CG of pediatric patients were more likely to say that their UCD patient had a very difficult time taking NaPBA, and drug adherence was particularly difficult for children without gastrostomy tubes. Responding physicians indicated that 25% and 33% of pediatric and adult patients, respectively, were prescribed less than the target dose, most often due to tolerability concerns (100%), administration difficulty (88%), side effects (75%), "milder form of UCD" (63%), high cost (38%), ability to control symptoms with diet (38%), and preference of NaBZ (25%).

3.5.2. Sodium benzoate

As reported by CG, only 17% of patients were receiving NaBZ at the time of the survey. Eight percent of patients reported receiving NaBZ. According to CG survey, the percent of patients reporting no side effects was non-significantly higher than for NaPBA (45%), with fewer patients reporting any side effects (28%, "yes, some"; and 0%, "yes, a lot"). When prescribers were asked about the possible reasons for non-adherence to NaBZ, the answers included "patients forget to take it" (71%), the dosing frequency (64%), the volume/amount (50%), difficulty swallowing (50%), side effects of medications (36%).

3.6. L-Arginine and L-citrulline: dosage, safety, and adherence

This category includes L-citrulline, L-arginine free base, and arginine hydrochloride 10% solution, taken by 46%, 10%, and 8% of patients, respectively. L-Citrulline was regarded as an 'effective' or 'very effective' therapeutic agent by 78% of patients. L-Arginine free base and L-arginine hydrochloride were called 'effective' or 'very effective' by 100% of patients. L-Citrulline was tolerated better compared to L-arginine free base and L-arginine hydrochloride: 81%, 50%, and 40% of patients, respectively. The most common reasons for non-adherence, according to the surveyed physicians, were "patient [forgetting] to take it" (~60–70%), dosing frequency (~40–50%), and the drug amount (~25–40%).

3.7. Formulas and nutritional supplements: dosage, safety, and adherence

Medical formulas and nutritional supplements include amino acid formulas (Cyclinex-1, Cyclinex-2, UCD-I, UCD-II, Essential Amino Acid mix), Duocal, ModuCal, Polycose, and Prophree. According to CG, 56% of UCD patients were on amino acid formulas (Cyclinex, UCD-I and II, and Essential Amino Acid mix). In general, over 72% of patients and 87% of CG reported that medical food was 'effective' or 'very effective' in controlling their UCD symptoms. Most patients tolerated the enteral nutrition well; 89% of patients and CG reported no side effects. Reported side effects were relatively mild and mostly confined to the gastrointestinal tract: nausea and vomiting decreased appetite, stomach distress, burning sensation in the mouth, headaches, and heartburn. Mixing medications (e.g. sodium phenylbutyrate) with medical foods may have confounded the reported frequency of gastrointestinal side effects in this category, but such mixing was not systematically evaluated in this survey. Among the reasons for amino acid formula non-adherence, ~35% of physicians named the volume, frequency, and difficulty taking it.

4. Discussion

Non-adherence to long-term drug and dietary treatment is a common problem in patients and families affected by inborn errors of metabolism. Studied examples include phenylketonuria and glycogen storage disease type 1a [12,13]. Similar to other metabolic diseases, non-adherence to prescribed drug dosing or dietary management in UCD patients may result in immediate and severe consequences. Thus, drugs that have the potential to improve adherence - due to formulation, tolerability, or dosing - could be seen as innovative in potentially improving patient care and clinical outcomes.

This survey systematically analyzed factors that could influence adherence to UCD dietary supplements and medications as potential contributing factors to HAC. Consistent with published reports [4], the most common cause of elevated ammonia was intercurrent infections, followed by dietary indiscretion and drug non-adherence. At the time of the survey, NaPBA was the only FDA-approved and the most commonly prescribed medication for UCDs (60% of patients). Eighty-six percent of patients indicated that NaPBA was effective or very effective. Nevertheless, only 25% of patients indicated that they never miss NaPBA. Reasons for non-adherence as reflected in the survey included

the amount of NaPBA (90%), difficulty swallowing the drug (81%), dosage frequency (71%), forgetting to take the drug (71%) and drug-associated side effects (67%). These results suggest that adherence can be improved by addressing the intrinsic properties of the treatment itself, including drug dosing, tolerability, and side effects. NaBZ, which was taken by only 17% of patients, was also viewed as effective by most participants, and adherence was similarly suboptimal.

Several limitations apply to this study. The survey used a self-report design, which is known to overestimate drug compliance [14]. It also did not attempt to collect precise information from medical records pertaining to clinical outcomes, such as frequency of documented HACs, ammonia levels or nutritional status which could have yielded statistical and/or clinically relevant differences between patients, CG and physicians. Nor did the survey systematically explore the effects of race and/or ethnic differences on drug compliance in order to identify potential socioeconomic factors affecting outcomes. As the survey was not a prospective study, it could not establish whether non-adherence influenced the frequency of HAC, hospitalizations or medical encounters. Also, because urea cycle patients often are prescribed more than one medication, a specific association between a non-adherence event and any given medication is difficult to establish.

The results of the survey nonetheless allow several conclusions. First, this survey, which was unique in that it queried not only patients but also their CG and physicians, demonstrated general agreement among these groups with respect to the effectiveness of various treatments. There was less concurrence between patients/CG and physicians regarding adherence, with physicians viewing their patients as less compliant than did patients and CG themselves. Second, treatments at the time of this survey, while viewed as generally effective, represent a significant burden to patients and families living with UCDs, with frequency of dosing, amount of drug and drug tolerability and side effects representing major reasons for drug non-adherence. Third, although not the major reported triggering factor for HAC, non-compliance was viewed by all respondents as an important contributing factor. Finally, the findings collectively reflect the need for development of less burdensome medical formulas and medications which would improve adherence and outcomes.

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