Development of Conceptual Frameworks and Patient-Reported Outcome Measures in Ornithine Transcarbamylase Deficiency

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BACKGROUND

- Ornithine transcarbamylase (OTC) deficiency is a rare inborn error of metabolism that results in high ammonia blood levels causing hyperammonemia. Hyperammonemia can present with symptoms of confusion, vomiting, coma, and consequently cognitive functioning impairments[1,2]
- Hyperammonemia can be life-threatening[3,4]
- The incidence of OTC deficiency is estimated to occur in one in 14,000 births[2]

OBJECTIVES

- The objective of this research was to develop disease-specific, content-valid patient-reported outcome measures (PROs) for use in OTC deficiency using a patient-centric outcomes assessment approach
- The development of PRO measures and hypothesized conceptual models for signs, symptoms, and impacts of OTC was achieved through reviewing relevant literature, key opinion leader (KOL) interviews, and patient interviews

METHODS

- Results from a targeted literature review, interviews with KOLs, and patient concept elicitation interviews were used to develop draft conceptual models and questionnaires
  - Mixed concept elicitation and cognitive interviews were conducted to debrief the draft questionnaires. Interviews were conducted 1:1 using a semi-structured interview guide
- All interviews were conducted with English-speaking patients after institutional review board/ethics approval
- Results from interviews were used to update the initial conceptual models and questionnaires

Figure 1: Overview of methods

Targeted literature review
A focused literature review (N = 49 abstracts) was conducted via Medline® to identify clinician- and patient-reported signs, symptoms, and impacts of OTC.

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Key opinion leader interviews (n = 3)
KOLs for clinician interviews were identified by the study sponsor.

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Concept elicitation interviews with adult patients (n = 2)
Following ethics approval, patients with OTC were recruited for interviews using a recruitment flyer.

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Development of preliminary conceptual frameworks and draft PROs
The conceptual frameworks were developed based on results from the literature review and KOL and patient interviews. The conceptual frameworks were used to develop items for pilot PRO assessments.

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Mixed concept elicitation and cognitive debriefing of draft PROs (n = 10)
Interviews included a cognitive debrief of the novel OTC-specific PRO assessments.
Measures were updated based on the results of interviews.

RESULTS

- The Hyperammonemia Indicator Questionnaire (HI-Q) was designed to collect patient-reported occurrences of symptoms of hyperammonemia (Figure 2a for the conceptual framework)
- OTC Deficiency Impact Questionnaire (OTC-D-IQ) was designed to collect patient-reported diet, emotional, physical, and sleep-related impacts of OTC deficiency (Figure 2b for the conceptual framework)

RESULTS, continued

- Ten mixed-concept elicitation and/or cognitive interviews were conducted with adolescent (n = 2) and adult (n = 8) participants to debrief the adolescent and adult version of the measures. Additionally, one child (aged 8) participated in an interview to debrief the child version of the measures
  - Despite the small sample size for child participants, results were still considered in conjunction with the adolescent/adult results to inform measure revisions
- Overall, the instructions, items, and response options for the HI-Q and OTC-D-IQ were interpreted as intended and reported to be clear and relevant
- Based on the results of cognitive interviews, the HI-Q Items 1–6 response scale was changed to assess concepts in terms of frequency rather than severity. Several concepts were removed from or identified for inclusion in the OTC-D-IQ (Figure 3)

Figure 2a: Hypothesized conceptual framework for signs and symptoms (HI-Q [Adolescent/Adult Version])

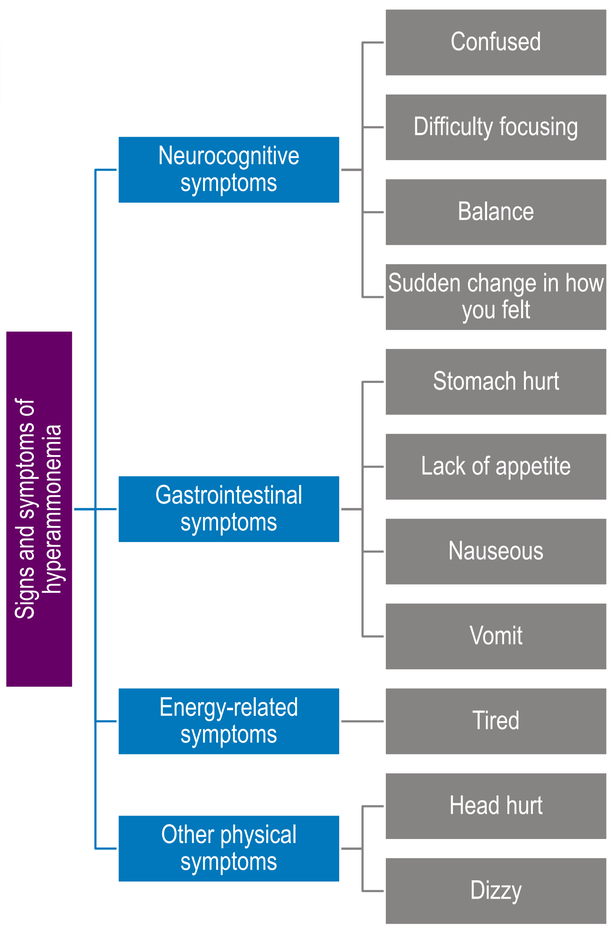

Figure 2b: Hypothesized conceptual framework for impacts (OTC-D-IQ) [Adolescent/Adult Version])

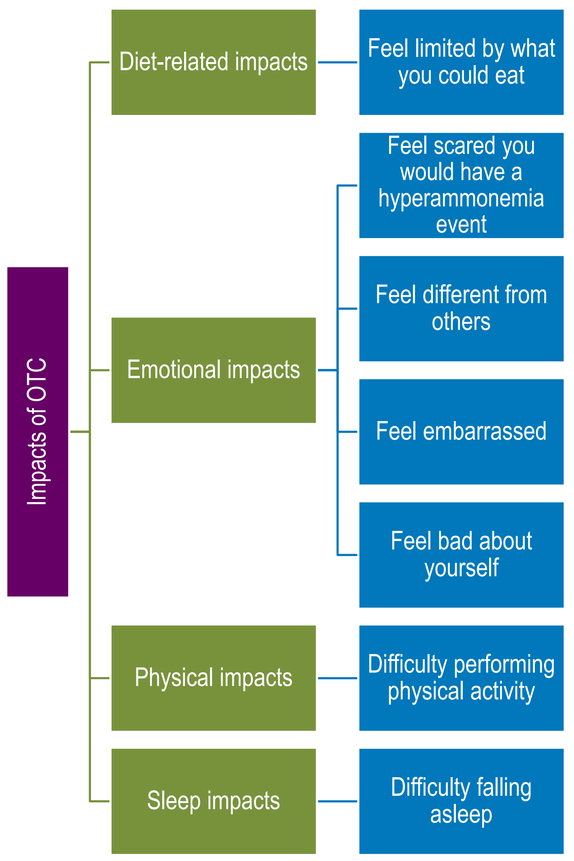

Figure 3: Overview of changes to HI-Q and OTC-D-IQ based on the results of the cognitive interviews

HI-Q	OTC-D-IQ
• Confusion	• Feel limited by OTC diet
• Ability to focus	• Eating food outside of restricted diet
• Balance	• Feel scared about having a hyperammonemia event
• Stomach pain	• Feel different from others
• Headache	• Feel embarrassed
• Tiredness	• Feel bad about yourself
• Loss of appetite	• Receive unwanted attention from others
• Nausea	• Difficulty performing physical activity*
• Vomiting	• Difficulty falling asleep*
• Dizziness	
• Sudden change in how you felt (e.g. feeling drunk or disoriented)	

Notes: *, Concept identified as missing and added after cognitive debriefing interviews.
Strikethrough indicates the concept was removed based on the results of cognitive interviews.
For both measures, the recall period is the past 24 hours and measure frequency (i.e., "how often") for all items except vomiting in the HI-Q which measures "how many times".
Response options for all items are: "never", "rarely", "sometimes", "often", "always" except for vomit where the respondent records the number of times.

CONCLUSIONS

- These PRO measures were developed with the PRO Guidance in mind and incorporated the flexibility encouraged by the Food and Drug Administration's Rare Disease Guidance[5,6]
- The results of the interviews support the content validity of the HI-Q and OTC-D-IQ.
- The OTC HI-Q and OTC-D-IQ are the only measures developed and tested for use in this population
- Future research includes psychometric evaluation of and corresponding revisions to the measures

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