The burden of pharmacological treatment on health-related quality of life in people with a urea cycle disorder – a qualitative study

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Abstract

Background

Urea cycle disorders (UCD) are a group of conditions of inborn errors of metabolism, typically presenting neonatally. Excess ammonia builds rapidly within the body, risking hyperammonemic episodes and potentially death. Long-term management of the condition includes restrictive protein consumption, pharmacological interventions and, in extreme cases, liver transplantation. Pharmacological treatments such as sodium benzoate and sodium phenylbuturate have proven effective but not without a multitude of negative attributes including poor taste, elevated volume and associated gastrointestinal discomfort that impacts on health-related quality of life. Glycerol phenylbutyrate (GPB) has recently become a widely available pharmacological treatment with early reports of improved qualities. The following study aims to explore the burden of pharmacological treatment on health-related quality of life in people with a UCD.

Results

9 carers of people living with a UCD were interviewed regarding their experiences of pharmacological treatment in relation to their, and their dependent’s health-related quality of life after transitioning to GPB. Three main themes were identified following data analysis: psychological health, physical health and social participation. Carers struggled with anxiety surrounding their dependent’s condition and the relentless battle of administering medication. Medication administration was perceived to have improved since the transition to GPB, alleviating distress for both carer and dependent. Issues involving schooling were commonly described, ranging from difficulties integrating their dependent into mainstream schooling and the impact of treatment on participation in school and extracurricular activities. Based upon participant’s experiences, it could be suggested that some burden had been relieved by the
transition to GPB. However, it appeared that the burden would persist despite treatment, owing to the continuing nature of the condition.

**Conclusions**

Adhering to a strict pharmacological regime caused immense stress for both carers and dependents, severely impacting on typical social activities such as eating at a restaurant or going on holiday. GPB was perceived to have alleviated some burden in terms of administration. Practitioners should consider these findings when making clinical decisions for UCD patients and the effect of pharmacological treatment on health-related quality of life. Emotional support resources should be made readily available to families to assist with daily living.

**Keywords:**
Urea cycle disorders, sodium phenylbutyrate, sodium benzoate, glycerol phenylbutyrate, quality of life, pharmacological burden, social, psychological health, physical health

**Background**

Urea cycle disorders (UCDs) are rare metabolic disorders caused by inherited deficiencies in any one of the six enzymes or two transporters of the urea cycle pathway [1]. The urea cycle normally converts ammonia into urea for excretion. However, in people with a UCD this does not happen and as a consequence, they face rapidly increasing ammonia levels that can be devastating to the body. Diagnosing a UCD early is critical to reducing mortality and potentially, permanent neurological damage [2]. Initial symptoms of the disease include lethargy, non-compliance to diet and abnormal motor function, which typically precedes the first hyperammonemic episode [3]. Whilst these symptoms often present in the neonatal period, there are cases of late onset in adult patients that have been triggered by a significant life event.
such as pregnancy [4]. Early research has illustrated that survival of UCD patients drops dramatically during the first 5 years of life after neonatal onset [5], however, there is an ever-increasing number of families who engage in long-term management of the condition owing to a growing number of treatment options [6].

UCDs are normally treated in a multifaceted way dependent on the severity of the disease. These methods include: strict dietary control involving heavily restricted protein intake, pharmacological interventions, and amino acid intake [7]. UCD patients are heavily reliant on drugs to control their ammonia. Two of the most commonly prescribed drugs, are sodium phenylbutyrate (NaPBA) and sodium benzoate, which scavenge excess ammonia from the body. Each treatment can be taken in a variety of forms including granules, tablets and liquid-based. Patients who have taken NaPBA orally have generally reported negative attributes such as: poor tolerability, extremely high burden of treatment (40 large capsules a day) and associated nausea [8]. These attributes impact upon drug adherence which, in the case of UCDs, can be potentially fatal [9]. Similarly, sodium benzoate has been known to provoke gastritis, making it difficult for patients to stomach this orally [10]. Given the reported problems with pre-existing drugs, health-related quality of life of patients and their parents could be significantly compromised. Research to date concerning health-related quality of life (HrQoL) in UCD patients has been sparse with research focussing on clinical outcomes such as ammonia levels and associated side-effects of medication. However, as survival rates have improved dramatically in people with UCD, there is a need to focus on improving HrQoL [6].

With regard to HrQoL, progress has been achieved in improving the tolerability of pharmacological interventions required to manage ammonia levels. Efforts have been made to change the method of administration to pre-existing medications. For example, administering sodium benzoate as an oral solution and presenting patients with various flavours has been shown to improve acceptance [11]. Glycerol phenylbutyrate (GPB; marketed as Ravicti®) has
demonstrated its safety and utility in controlling ammonia levels in UCD patients since first approved by the FDA in 2013 [12,13]. Further preliminary research has demonstrated that treatment-related symptoms, such as nausea and abdominal pain, have decreased significantly once patients transitioned from NaPBA to GPB in both adults and children [14].

The burden of pharmacological treatment is typically high for UCD patients who must follow strict dosages and times, often coupled with a rigorously planned protein-restricted diet. A recent study that analysed data across international centres demonstrated that the burden of disease and the burden of dietary restrictions contributed significantly to impaired HrQoL [15]. The burden on both child and carer is such that many families consider the burden of disease a core deciding factor when considering whether their dependent should have a liver transplant rather than continue with medical management [16]. Research specifically into burden of pharmacological treatment has been sparse and thus requires further investigation in relation to HrQoL. As there are several treatment options available (NaPBA, sodium benzoate, GPB), capturing a breadth of experience utilising different drugs is pertinent. The psychosocial impact of pharmacological treatment has yet to be elucidated in the context of UCDs, where preliminary clinical evidence points toward elevated burden associated with particular treatments [8,14].

HrQoL has been explored in UCD patients previously but primarily through survey studies in a cross-sectional manner, leading to a paucity of qualitative data concerning HrQoL in UCD patients [17–19]. Interviews, as opposed to surveys, allow participants the freedom to express their experiences, within context, which may not have been previously considered [20]. Adopting a qualitative approach to understanding HrQoL of UCD patients would achieve deeper insight into the lived experiences of the condition and treatment regime patients and carers must follow on a daily basis. The impact of pharmacological management on HrQoL in UCD patients who have transitioned from either NaPBA or sodium benzoate onto GPB has not
been investigated. By gaining an understanding of how pharmacological management impacts HrQoL, practitioners will be better informed when deciding patient’s pharmacological treatment regime, considering the subsequent impact of the drug on HrQoL and which treatment approach would be best suited for each patient. Understanding the wider impact on other elements of HrQoL would also inform practitioners regarding the specific challenges patients face that may not have been previously considered beyond the immediate impact of drug intake, such as social and psychological implications. This study aims to investigate the burden of pharmacological management and subsequent impact on HrQoL in UCD patients and their carers.

Method

Design

A qualitative design was selected using semi-structured interviews to address the research aim.

Ethical approval was obtained from Manchester Metropolitan University Faculty Ethics Committee, UK (Ref: 10306). The study is reported in accordance with the consolidated criteria for reporting qualitative (COREQ) research [21].

Participants

Participants were recruited utilising a purposive sample, facilitated by Metabolic Support UK (MSUK). Participants were included if they or someone they care for had received a formal diagnosis of a UCD, they lived in the UK and had transitioned onto GPB as their primary form of treatment for the condition. Patients were excluded if they were diagnosed with inborn error of metabolism other than UCD or if they did not live in the UK. Given that it is estimated that UCD affects 2100 patients across Europe [22], the research team were aware that identifying and recruiting sufficient participants located in the UK would be challenging. Therefore, a gatekeeper at MSUK was used to facilitate access to participants. A sample size of 10-15
participants was sought for the study or until data saturation was achieved. Data saturation can be described as the point at which new information or data provokes little or no change to subsequent codes and themes [23]. The gatekeeper advertised the study in a private social media group that is well-established in the UK for parents and carers of patients with UCD. The advert stated that either carers or patients were eligible to take part in the research. Recruitment for the study continued concurrently whilst interviews were being conducted, until data saturation was achieved. Members of the group were encouraged to get in contact with the gatekeeper if they were interested in participation once they had reviewed the brief advertisement. Emails containing expressions of interest were passed onto the research team who provided a participant information sheet and consent form to potential participants. Informed consent was obtained prior to undertaking the interviews.

Data collection

Semi-structured telephone interviews were arranged with participants and conducted by a single researcher from the team (DB). The medium of telephone was selected owing to the geographically dispersed nature of the sample. Telephone calls mimic the format of a semi-structured interview, whereby the caller adapts and reorders questions in alignment with the topic of discussion [24], lending itself as an appropriate medium for this study. An interview guide was developed from a rapid scoping review of the UCD literature, coupled with expertise from the research team. The interview guide was then reviewed by the gatekeeper from MSUK and a carer of a person living with UCD to ensure its appropriateness. The final interview guide was arranged into three topics: living with UCD, HrQoL whilst utilising previous treatment(s) and HrQoL whilst taking GPB. A semi-structured approach to the interview, afforded the researcher scope to explore elements of the participants’ lived experience that may not have been outlined in the interview guide. All interviews were digitally audio recorded and transcribed verbatim.
Analysis

Thematic analysis was conducted on written transcripts to elucidate pertinent aspects of participant’s lived experience. The six phases of thematic analysis outlined by Braun and Clarke [25] were followed to facilitate methodological rigour. Written transcripts were read multiple times, immersing the researcher with the raw data prior to initial coding taking place. Codes were arranged into sub-themes and themes and reviewed by two researchers from the team (DB, GY), refining through discussion. Any conflicts were duly resolved with the help of the third member of the research team (FF). NVivo software was used to organise transcripts, codes and themes accordingly. Analysis was performed iteratively throughout data collection as interviews were completed across a 3-month period owing to practical constraints, such as parents struggling for time during school holidays. This also allowed the research team to understand when data saturation had been achieved.

Results

Nine participants completed interviews across a 3-month period in 2019. All participants were carers for a dependent living with UCD. All dependents with UCD had transitioned from either NaPBA or sodium benzoate onto GPB. Demographic information relating to the UCD patients can be found in Table 1.

Table 1. Demographic data of UCD patients (all interviews undertaken with carers)

| Mean age | Sex | Previous treatment |
|----------|-----|--------------------|
| 12.44    | M = 7 | *Sodium phenylbutyrate* = 5 |
|          | F = 2 | *Sodium benzoate* = 4 |
Analysis of the data demonstrated that data saturation had been reached in order to answer the research question. Three themes were developed from the data: psychological health, physical health, and social participation. Several subthemes were identified within each of these themes and have been used to present the findings along with anonymised verbatim quotes from participants.

**Theme 1: Psychological health**

**Administration**

Managing UCD requires constant monitoring and high volumes of medication. Participants have historically relied upon either sodium benzoate or sodium phenylbutyrate to manage their dependents’ ammonia levels. However, participants described a multitude of negative components associated with these, ranging from high volume (“20mls was quite a large syringe” P2), a pungent smell (“it smelt absolutely terrible…” P9), unpalatable taste (“he used to complain that it burnt…” P8) and nausea (“after having it…he had tummy ache” P3). These factors converged in a way that rendered administration of the previous treatments highly challenging for the carer and distressing for the patients. The challenge of giving the medication to their dependent was described by a large number of participants:

“I just forced him, you had basically hold him down and force it into him, that’s was what you had to do even whenever we were in hospital that’s what we were just told “he has to take this” and we were having to hold him literally, which obviously caused a lot of distress for us and caused a lot of distress for him and distress around us, you know it’s just not a nice thing to have to do.” (P6)

The psychological burden of having to restrain their child during administration was extremely high for the UCD patient, the carer administering the drug and onlookers such as family members. A number of carers resorted to spacing the doses out to ensure that the medication
was taken by dripping smaller quantities across the day: “we used to literally just drip it in, because that was the only way we could get him to tolerate it”, P1. The specific administration times also presented a major inconvenience for carers:

“It did require a very structured process of the set times and so, you know, there were days when at 9 o’clock at night all you want to do is go to bed but actually you can’t. Or you’ll end up going to bed and setting the alarm to get up at 11 o’clock to give [patient] his meds.” (P2)

The transition to GPB had alleviated the numerous challenges associated with administering previous treatments for many participants. GPB was reported to possess positive qualities in comparison to previous treatments including: better taste (“he said it tastes like strawberries…”, P8), reduced volume (“it’s a lot less, it’s just easy having a little syringe…”, P3) and reduced sickness (“I can’t knowingly say he’s took it and vomited either.”, P1). The perceived drastic improvement in medication led to less apprehension from patients when taking their medication. Some carers also noted how GPB is received ready to administer, facilitating administration: “we haven’t got all that worry of making sure it’s made up to go anywhere” (P1). A recurring analogy used throughout by a few participants was the “battle” of administering medication on previous treatments, and noted how this battle had either been reduced greatly, or eliminated altogether after the transition to GPB:

 “…we don’t have battles that we had sometimes three times a day. I can give it him on an empty stomach, you know, if we’re late with a dose or for some reason we haven’t got it next to us for some reason, which means we can be a bit more relaxed. It’s just a bit less stressful and less worrying.” (P3)

The rigorous schedule that parents had to follow when giving medication to ensure that ammonia levels are stable were not as rigorous when taking GPB. Given GPB’s slow release
capabilities, carers felt more at ease giving medication slightly later or earlier: “…we now give [patient] his medication at 10 o’clock at night before I go to bed rather than my wife going to bed and I’m having to stay up another hour” (P2).

Emotions – Worry, fear, loneliness & happiness

For patients and carers living with UCD, the daily challenge of managing the condition and navigating a “normal” life led to substantial levels of worry. Especially following diagnosis and in the early stages of the condition, the uncertainty of how their dependents’ condition would fluctuate wasperturbing for all participants. One participant described living their life on “a knife’s edge” and taking it “day to day” (P9). Worry was especially prominent concerning previous treatments for a number of participants, owing to side-effects and problems administering the old drug. Sickness associated with the old treatments also led to worry in carers:

“he instantly felt sick, and that was something that we used to worry a lot about, because it made the whole thing a lot worse...” (P3)

Not only was nausea a worry in itself, carers also had anxiety surrounding whether they should re-administer medication after vomiting. When compared to the degree of worry experienced on the new treatment Ravicti, some participants reported a burden being lifted given that administration was significantly less challenging:

“The Ravicti [GPB] is fine, it’s a tiny amount, he can drink water after it it’s gone. So yeah, that was a real weight off our mind that it was a great medicine really.” (P8)

Closely linked to the feeling of worry was the notion of fear, experienced by both the primary caregiver and external onlookers. UCDs are extremely rare metabolic disorders, leading to both misunderstanding and a general lack of understanding from those who encounter it. The severity of the condition was especially concerning with a few carers reluctant to let their
dependent be under another party’s temporary care as they felt that others do not truly comprehend the importance of monitoring their dependents’ condition:

“I think (if it’s) outside the unit, it frightens people. Cause you have to tell people what they might have to deal with…” (P1)

The condition also led to concerted feelings of fear from the carer themselves. Some carers stated feeling fearful of their child’s condition as they constantly anticipated possible complications. One participant described their apprehension over returning their child to bed after they had been unwell “…in case he would get sick” (P3). A clear link between worry and fear was observed, two negative emotions that impacted on a plethora of life events. Important to note was the pervasive nature of these emotions which, some argued, would never change owing to the relentless battle with the condition as “that’s just the UCD life I think.” (P5), irrespective of the medication that their dependent is taking. Caring for a dependent with UCD led to a couple of participants expressing their loneliness. The perceived lack of understanding from others contributed to a feeling of isolation for most participants: “It’s quite lonely. There’s nobody I can turn to that understands exactly what I’m going through” (P4).

Whilst negative emotions appear to be an ever-present when managing a chronic life-threatening condition, positivity was expressed by a number of participants in relation to their transition to GPB. This was related to the burden of administration being reduced considerably leading to happier carers and ultimately, happier patients:

“he’s even happier now that he doesn’t have to stomach the Benzoate. Yeah, so you know, he’s happy.” (P7)

“it’s good for me not to see my son struggle taking the drug and that is really good to see. My quality of life is the same as before, but obviously not seeing your son struggle is brilliant.” (P7)
**Theme 2: Physical health**

**Overall condition**

As UCDs are particularly volatile in nature, managing ammonia levels was a constant for the family unit. A few participants, with varying levels of success, described ammonia levels on previous treatments. For some, they felt that the UCD was managed appropriately with the previous treatments, whilst others reported slightly elevated ammonia levels:

> “it had been taken up to around the 80’s on the sodium benzoate but it was down to the 40’s and it has hovered around between 40 and 60 since, which is a good level.” (P6)

A number of participants also noted how their dependents’ ammonia levels have reduced since the transition to GPB. They felt that the slow release properties that GPB possesses controls ammonia levels in a more stable manner: “since we’ve been on Ravicti [GPB] her ammonia levels have been the best they’ve ever been” (P4).

**Development**

The effects of elevated ammonia in the blood is highly damaging for the patient. One participant specifically referenced how they felt that the sodium benzoate inflicted damage on their child and subsequently impacted their development:

> “I think for all the good that benzoate was doing when it was high in the body, when it was low, that damage was being done and that damage was being permanent…” (P2)

The same participant does note that, since their child has transitioned onto GPB, they felt their development had improved dramatically. This improvement had led to a substantial improvement in their quality of life, as the carer felt that the patient would better comprehend experiences outside of the family home:
“we’re taking him to the London Eye next week and then onto the aquarium for a day out because we understand, we feel that he will comprehend some of what he’s seeing.”

(P2)

Theme 3: Social participation

Schooling

Managing the condition had, for all participants, impacted upon schooling at one point or another. Patients and carers experienced a plethora of schooling-related issues related to pharmacological management such as: reduced attendance, managing medication, lack of support and difficulty attending extracurricular activities. For example, one participant described how their child’s attendance at school “stands at 56%” (P4), due to the complications experienced as a result of the UCD and associated medication. Constant nausea and subsequent sickness after medication was the main contributing factor to non-attendance in this instance. Not only does sickness impact on attendance but “the number of [hospital] appointments” (P6) that patients attended also reduced attendance at school.

In terms of the school’s involvement with managing the condition, participants had had varying levels of success in communicating the importance of rigorous maintenance in terms of medication and diet. Problems had arisen regarding the school’s involvement in overseeing patient’s strict dietary restraints and the administration of medication in a timely manner. One participant outlined how they felt the school simply did not understand the true nature of the condition and underestimated how serious a missed dose may be:

“We’ve had instances of missed medication where I’ve been called to say “really sorry but we completely forgot to give him his medication and does he need to have it or can he have it when he gets home?” The seriousness of the condition has never really hit home.” (P8)
This participant also described feeling as if she were perceived as “neurotic” for monitoring his diet so closely, especially when the school was looking to give the patient food that other children were consuming at the time: “we used to have comments like “oh you need to loosen up a little bit you’ll give him an eating disorder” (P8). Another participant remarked that the transition to GPB had enabled greater participation in extracurricular activities and school trips:

“Because he doesn’t have Ravicti [GPB] now at 12 o’clock so if he has a school trip he’d have it 8 o’clock in the morning his next dose would be when he comes home at half three. That means during the day he can take a simplified medication.” (P8)

The participant noted that prior to the transition to GPB, they had to pack sodium phenylbutyrate with an ice pack to ensure it was stored at a temperature under 26 degrees, ready for administration. The transition to GPB had eliminated the midday dose, streamlining the patients’ schooling.

**Family & friends**

The management of the UCD was not limited to affecting the patient. The ramifications of the condition placed an emotional toll on family members including parents and siblings of the patient. One participant remarked how their daughter who’s sibling lived with UCD “had to start to cope with staying at friends’ houses at the last minute quite young... because we were in hospital for a few days” (P3). The battle to maintain positive emotion amongst multiple children, where the UCD patient must be monitored on a regular basis, is inevitably difficult.

The pressure that families feel to share tasks when looking after the patient is also exceptionally high. Given the relentless monitoring schedule that carers must engage with to maintain their child’s health, parents shared the load to ease the burden on the family unit:

“it might mean us having to, kind of, split our time, and I go away with [patient] and do stuff, dad goes away with [sister], and vice versa and then swap over.” (P5)
“often we’d take it in turns we’d pass the imaginary baton…” (P8)

The sharing of the load was also fairly restricted to within the immediate family unit as tasks and practices required when looking after the patient, such as the administration of highly specific doses of medication, were difficult for those unfamiliar with the condition. A number of participants recalled the issues they had encountered when trying to involve family with caring responsibilities.

“I just had the whole burden really and we didn’t have a lot of local family to support us, and the ones that were local didn’t quite understand and never visited us in hospital or nothing…” (P5)

One pertinent account relates to a carer’s attempts to take their dependent to the park to play. Owing to the patient’s ongoing illness and negative experience with the previous treatment before GPB, this was almost impossible: “…whenever he got to the park he got straight off the trike and vomited, he was always very nauseous and very sick, he would have vomited every day” (P6). The parent described how, now that the patient had transitioned onto Ravicti, trips to the park were possible and even frequent:

“he would maybe be out on his wee bike or whatever and he would just be sick. And as soon as he changed over to Ravicti [GPB] this sickness completely stopped.” (P6)

Practicalities & planning

The treatment regime that patients follow normally included: frequent medication, dietary restriction and hospital appointments. Balancing all of these aspects could be challenging, and the practical facets of each presented novel challenges for carers involving detailed planning and preparation for even small trips outside of the home. This ranged from being extremely cautious when eating out (“we have to check in advance what’s on the menu”, P1) to packing additional items to make trips out of the home easier should the patient become unwell (“I
used to carry a spare sheet along in my change bag when she was born, because she would vomit that often”, P5). Two participants noted that holidays abroad were now practically impossible, owing to the plethora of considerations and paperwork they would have to complete to ensure a safe trip: “I don't have the courage to go abroad because I don’t know what the medical..., where they are or how capable they are or getting the drugs through customs...” (P7). Ensuring that there was enough medication prepared for a trip out was also a barrier to engaging in activities outside of the home: “…going out's a minefield you're constantly checking have we got medication?” (P9). However, a few participants mentioned that, since the transition onto GPB and the decreased dosage, trips out of the house have become a lot easier:

“So [patient’s quality of life] dramatically because it’s taken away that midday dose, so for his medication to be simpler, it was quite difficult before you’ve got four different medicines you’re trying to mix and juggle, it’s really simple what he has now during the day.” (P8)

Again, whilst GPB has contributed to less preparation (“it’s easier and you haven’t got all that making it up...”, P1), one participant poignantly noted that the planning and practicality would persist irrespective of the treatment their dependent received:

“It's just always going to be a constant, I think, I don't think any change in medication's going to help. I think it's just it's always going to be like that.” (P5)

Discussion

Living with a UCD can be extremely debilitating depending on the severity of the condition. Intense pharmacological treatment, coupled with strict dietary control, means that both carers and patients are in a constant state of monitoring. Whilst HrQoL has previously been investigated primarily through survey studies, which can be limited in exploring experiences
in-depth within context [17,18,20], this study successfully explored the burden of pharmacological treatment and subsequent impact on HrQoL in UCD patients and carers. After completing semi-structured interviews with carers of 9 participants who had successfully transitioned from one medication to another, themes concerning psychological health, physical health and social participation emerged. Both positive and negative aspects were described by participants in relation to the transition from either NaPBA or sodium benzoate to GPB. Patients and carers were affected simultaneously in a variety of ways during pharmacological treatment and transition, demonstrating the burden placed on both the patient and the individual administering medication.

The psychological impact of managing a UCD through pharmacological intervention, drawing from the lived experience of both patients and carers, was exceptionally high. Administration emerged as one of the main psychologically challenging aspects of pharmacological management. Linked implicitly to the negative attributes attributed to UCD treatments [14], adhering to a strict administration regime placed significant psychological strain on both patients and carers alike. One poignant account described the act of having to physically restrain their dependent whilst taking sodium benzoate to ensure that the medication was taken as prescribed. For many, the most challenging aspect of pharmacological management was the administration of the drug. Previous research has illustrated how negative attributes of a drug can be significant barriers to adherence in patients with inborn errors of metabolism, such as the taste of the medication, the frequency of administration and associated side effects [9]. The problems associated with medication in the current study population (tolerability, dosage, nausea and smell), and the patient’s general reluctance to take their medication, were often attributed to elements such as poor taste, burden of treatment and subsequent nausea experienced after the medication had been administered. The “battle” that many carers used metaphorically induced a deep sense of worry, whilst UCD patients experienced trepidation at
administration times. It is important to note that the administration “battle” was alleviated somewhat after the transition onto GPB. In line with research describing the more positive elements of GPB [14], relying on GPB as primary pharmacological treatment could provide some respite for carers.

Negative emotions were frequently described and alluded to by participants, illustrating the multifaceted nature of the condition and pharmacological regime. Fear was an emotion both encountered and experienced by carers. Given the rigorous pharmacological management regime that is followed, many acquaintances, friends and family were scared to take full responsibility for the UCD patient through fear of mismanaging the condition. The psychological and pragmatic burden of this was substantial, with parents and carers shouldering the entirety of care responsibilities. Coupled with this were feelings of loneliness owing to the rarity of the condition and misunderstanding from others, as well as inordinate amounts of worry, especially when patients experienced side effects that impacted upon subsequent administration times and doses.

The primary aim of pharmacological management in UCD patients is to maintain stable ammonia levels, thus preventing potential complications such as hyperammonemic episodes. The struggle to maintain safe ammonia levels was described in great detail by participants. Participants remarked how, on the initial treatment prior to the transition to GPB, ammonia levels were higher and would fluctuate more frequently. The impact of elevated ammonia levels in UCD patients culminates into frequent hospitalisation and added burden for both patient and carer. A number of participants noted that their dependent’s ammonia levels had reduced and become more stable following their transition onto GPB. This mirrors research suggesting that ammonia levels are significantly lower on GPB as compared to NaPBA, with reduced instances of abnormal values [26]. The consequential effect of improved ammonia levels for participants meant reduced hospital visits and alleviated worry for the carer. Again,
it could be suggested that relying primarily on GPB as the main mode of pharmacological management could reduce burden on both patients and carers by reducing engagement with tertiary care and a reduction in negative emotions experienced, such as worry.

The effect of pharmacological management manifested itself in severe impacts on social participation including schooling, family events and holidays. Families described how difficult managing relationships with the UCD patient’s school was, as some schools failed to fully understand the severity of the condition. Whilst providing schools with a day-to-day management plan is recommended [10] and was commonly reported by participants, their experiences suggested that knowledge underpinning pharmacological treatment for UCD patients in teachers and school staff was sorely missing. The rigorous nature of the day-to-day plan, above and beyond teacher’s daily routine, seemed to cause major inconvenience which ultimately impacted upon UCD patient’s wellbeing. Moreover, participants had experienced instances where their dependent was unable to participate in extracurricular school activities, or even mainstream education despite carers feeling that this would benefit their dependent socially. This mirrors previous research where parents of UCD patients possessed great concern over the social challenges their child faced [27]. The disparity between schools and parents is evident, suggesting that further work should seek to bridge the gap between education providers and the UCD community to better support children both in their education and in their social wellbeing.

There are limitations to this study. A small number of participants were relatively early in their transition from previous treatments to GPB (within 6 months), meaning that they may not have had extensive experience in discussing long-term effects of GPB on HrQoL as opposed to previous treatments. Given GPB is a relatively new treatment option in terms of accessibility, determining the long-term impact of GPB on HrQoL may only be attainable in time when more UCD patients are engaged with GPB as their primary treatment option. Coupled with this,
participants were primarily interviewed during the summer months during school holidays. For some, their child had yet to begin formal schooling. Understanding the full range of schooling challenges is imperative to improving the apparent misunderstanding that parents’ encounter on a regular basis.

The sample of participants in this study cared for UCD patients who were primarily of school age. Evidence suggests that mortality rates in neonatal patients is fairly high compared to healthy counterparts [28] suggesting that a significant number of UCD patients do not survive through their early years without strict pharmacological management. Whilst life expectancy has yet to be assessed in times where greater treatment options are available, future research should attempt to recruit older UCD patients to understand HrQoL in later stages of life and for those who may be living in a more independent fashion. Similarly, experiences of living with UCD could be different between the different types of metabolic deficiency, such as between ornithine transcarbamylase (OTC), carbamoyl phosphate synthetase 1 (CPS1) and argininosuccinate synthetase (ASS). Segregating participant’s dependent on the severity and type of condition could elucidate any specific challenges that may exist between conditions and mode of drug intake.

**Conclusion**

This study has illustrated the multifaceted and persistent challenges both parents and children face in relying on pharmacological treatment to manage UCDs. Improved understanding of HrQoL in UCD patients under pharmacological management will facilitate decision-making processes for those in clinical practice to treat the condition in a way that is least detrimental to HrQoL. Considering the impact of pharmacological management on all parties involved in treating UCD, HrQoL should be a core consideration alongside the patient’s ammonia levels. The results of this work will facilitate future work that could provide both pragmatic and
emotional support to families living with UCD. Findings suggest that transitioning to GPB could alleviate some pragmatic challenges faced by families but, ultimately, that battling the condition will persist throughout the UCD patient’s life. For this reason, greater attention should be placed on providing families with resources to cope with the daily challenges that the condition presents, such as emotional support and respite for carers. Finally, outreach work should be performed with key locations, such as schools, to increase understanding of the condition and alleviate the considerable burden carers face on a daily basis.

**Abbreviations**

UCD: urea cycle disorders

NaPBA: sodium phenylbutyrate

GPB: glycerol phenylbutyrate

HrQoL: health-related quality of life

MSUK: Metabolic Support UK

OTC: ornithine transcarbamylase

CPS1: carbamoyl phosphate synthetase 1

ASS: argininosuccinate synthetase

**Declarations**

- Ethics approval and consent to participate - Ethical approval was obtained from Manchester Metropolitan University Faculty Ethics Committee, UK (Ref: 10306). Participants were presented with a participant information sheet to consider prior to indicating their consent. Completed consent forms have been retained by the research team.
• Consent for publication – Not applicable

• Availability of data and materials - The datasets generated and/or analysed during the current study are not publicly available due to the data containing personally identifiable information, but are available from the corresponding author on reasonable request.

• Competing interests – The authors declare that this study was funded by Swedish Orphan Biovitrum (SOBI) pharmaceutical, the company that was authorised to distribute Ravicti (GPB) at the time when the study was conducted. The writing of this manuscript was funded by Immedica Pharma AB, the company who is currently the marketing-authorisation holder of Ravicti (GPB).

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• Authors' contributions – GY and FF designed the study, contributed to data analysis, and contributed to drafting and revising the manuscript. DB acquired the data, performed data analysis and contributed to drafting and revising the manuscript. All authors have approved the submission of the final manuscript and have agreed to be personally accountable for the author’s own contributions.

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