THE EXPERIENCES OF PATIENTS WITH WILSON DISEASE IN PUNJAB, PAKISTAN: A CONCEPTUAL MODEL BASED ON QUALITATIVE RESEARCH

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ABSTRACT

Background: Wilson disease (WD) is a rare disease wherein copper accumulates in tissues, leading to hepatic degeneration, neurological impairments, and psychiatric symptoms. This study aimed to characterize the experiences of patients with Wilson Disease (WD) and develop a conceptual model containing key symptoms and impacts of the disease.

Results: A targeted literature review was conducted to develop a preliminary conceptual model of Wilson Disease (WD) that was subsequently refined through one-on-one interviews with 3 Wilson Disease (WD) clinicians and finalized following concept elicitation interviews with 11 patients and 11 caregivers. The literature review returned 20 articles, from which 35 concepts (25 signs/symptoms and 10 impacts) were selected for inclusion in the preliminary conceptual model. After interviews with clinicians, the model was expanded to include 25 signs/symptoms and 10 impacts. The final comprehensive conceptual model developed after interviews with patients included 54 symptoms in total (n = 22 hepatic, n = 19 neurological, n = 13 psychiatric), and 21 impacts. Across symptoms, patients reported a high level of bother, with approximately 49% of symptoms reported by patients having an average peak bother rating of ≥ 7 out of 10 (10 = most bothersome). Patient interviews identified 2 subgroups of patients: those who experience neurological, psychiatric, and hepatic symptoms and those who experience mostly hepatic and some psychiatric symptoms, but no neurological symptoms.

Conclusions: This research underscores the substantial multisystem symptoms and impacts that patients with Wilson Disease (WD) describe as highly bothersome in their lives. Hepatic symptoms emerged as especially common and important to patients with Wilson Disease (WD), possibly beyond what is commonly understood in research and clinical practice. Further, the description of 2 distinct patient groups may help to inform patient management and support more targeted drug development processes neurological symptoms.

Keywords: Wilson Disease, Hepatolenticular degeneration, Liver Transplant, Neurological impairments, Psychiatric issues.

INTRODUCTION

Wilson disease (WD) is an inborn autosomal recessive disorder of impaired copper (Cu) transport. Over time, Cu accumulates in liver, brain and other tissues, resulting in progressive organ damage and dysfunction that can vary from patient to patient [Delvi, 2014]. Diagnosis can occur in childhood, but in some cases may be later in life [Yamaguchi et al. 2020]. Clinical prevalence estimates for WD range

from approximately 1 per 30,000 to 1.5 per 100,000 worldwide [Schaefer et al. 2016] although the frequency of genetic markers for WD may be higher in selected regions such as in some Asian communities, where geographic isolation has given rise to increased prevalence due to con-sanguineous transmission [Brewer and Emeritus, 2015]. Among people with an identified mutation, disease manifestation will be present in approximately 50% of individuals [Czlonkowska et al. 2018].

Management of WD often requires a multidisciplinary approach that combines hepatology, neurology and psychiatry specialists, given the potential involvement of all 3 systems in the clinical presentation of patients with WD. Currently available therapies for the treatment of WD include the general chelation therapies D-penicillamine and trientine, which non-specifically chelate Cu and promote urinary Cu excretion. In addition, zinc (Zn), which blocks uptake of dietary Cu, is used for maintenance treatment. These therapies need to be dosed 2 to 5 times per day and should be taken in the fasted state. These therapies also have high rates of treatment discontinuation due to poor tolerance [Dress et al. 2021]. Common adverse events include gastric discomfort, anemia, elevated liver function tests, proteinuria, autoimmune disorders, bone marrow suppression, and neurological worsening. Although liver transplant is an option for patients with predominantly hepatic manifestations, its use is debated in patients with WD and progressive neurological deterioration. Regardless of presentation, patients with WD require life-long therapies [Poujois et al. 2018].

The impact of WD to patient's health-related quality of life (HRQoL) has not been extensively assessed. However, the few published studies focusing on the humanistic burden of WD show the negative impact of the disease on HRQoL of patients and their caregivers. Patients with WD are at risk of depression and have been reported to have low HRQoL as assessed with the 36-Item Short Form Health Survey (SF-36), particularly when patients have primarily neurological or psychiatric manifestations (for instance, anxiety and depression) [Bandmann et al. 2015]. Increased psychiatric symptoms such as depression and anxiety have a substantial impact on patient quality of life. Other psychiatric and neurological features of the disease, including emotional and behavioral dyscon- trol, limit the ability of patients to participate in socialization and other daily activities. HRQoL is worse among patients with decreased functional mobility and limited ability to interact within their environment and society. In patients with WD, the physical domain of the World Health Organization Abbreviated Quality of Life measure (WHOQoL-BREF) has been shown to be inversely correlated with treatment duration and disease severity. In addition, patients with WD scored significantly worse on the generic 12-Item Short Form Health Survey (SF-12) tool when compared to controls without WD selected from an Italian epidemiological database used to study health conditions. Sex differences in WD have also emerged that may affect HRQoL as women with WD report significantly lower HRQoL scores than men [Schaefer et al. 2016].

OBJECTIVE OF THE STUDY

The objective of this study was to explore the experiences of patients aged 12 years and older with Wilson Disease (WD), and to develop a conceptual model representing the key symptoms and impacts of Wilson Disease (WD).

MATERIALS & METHODS

The study was conducted in several steps. A targeted literature review (TLR) was first conducted to develop a preliminary conceptual model of Wilson Disease (WD). This model was refined based on the findings from one-on-one interviews with clinicians actively treating people with Wilson Disease (WD) and was then finalized following input from one- on-one interviews with patients and caregivers.

One-on-one in-depth qualitative interviews were conducted with 3 expert clinicians recruited based on their practice area and experience in the management of patients across the lifespan with Wilson Disease (WD) in Lahore, Punjab. One clinician was interviewed within each relevant subspecialty neurology (Service Hospital, Lahore), psychiatry (Children Hospital, Multan), and hepatology (Children Hospital, Lahore). Additional selection criteria included having a clinical practice in the Lahore (with> 10 years' experience) and frequently seeing patients in their practice and managing their Wilson Disease (WD) care.

Interviews were conducted face to face and lasted approximately 60–75 min. Interviews were led by a trained interviewer, and a semi-structured discussion guide was used to facilitate the conversations. Clinicians were first asked to discuss, without prompting, the signs, symptoms and impacts patients and their caregivers report, and then any additional signs, symptoms and impacts that they observe. After unprompted discussion, clinicians were probed on any remaining concepts from the preliminary conceptual model, or concepts that had been identified through social media listening. Interviews were recorded and subsequently transcribed for analysis. Insights from clinician interviews were used to revise the preliminary model to an interim conceptual model.

Semi-structured concept elicitation (CE) interviews were conducted with 11 patients with WD and 11 caregivers. Patients were recruited from the Lahore (n = 8) and Multan (n = 3). Screening criteria was set such that participating patients had to have a clinical diagnosis of Wilson Disease (WD) and be 12 years of age or older in the Punjab (Lahore & Multan). Patients also had to report experiencing symptoms due to Wilson Disease (WD) or the treatment they were receiving for Wilson Disease (WD) during the last4 months. Additional details on the selection criteria are provided in the Additional file 1: Table S3.

The interviews were structured in three sections and were designed to last approximately 90 min. The first section focused on general demographic questions. The second section explored the patient journey with WD, including time since diagnosis and treatment history. The third section focused on the patient experience with WD (signs, symptoms, and impacts). Signs, symptoms and impacts of WD, currently and previously experienced, were first obtained unprompted, or spontaneously, followed by more prompted exploration of signs, symptoms and impacts using probes for discussing those concepts that had not yet been mentioned by the patient but which had been previously identified from the TLR and clinician interviews. For each concept currently experienced, patients were asked to provide a current peak bother rating on a scale from 0 (not at all bothered) to 10 (greatly bothered). For each concept previously experienced, patients were asked to provide a past peak bother rating using the same scale. Ratings were used to help quantify the effect of each concept throughout the patient's disease history.

The CE interviews for the current study were conducted in three waves (Wave 1, n = 4; Wave 2, n = 4; Wave 3, n = 3). Patient transcripts were analyzed chronologically after each wave to assess whether

concept saturation had been reached. Saturation of concepts was defined as the point at which no new information was forthcoming from ensuing patient interviews. Saturation of concepts was determined to be adequate after the third wave of interviews (i.e. after 11 interviews).

Interviews were audio-recorded and subsequently transcribed for analysis using ATLAS.ti v8 qualitative analysis software. Coders reviewed the transcripts to identify relevant concepts by tagging the relevant text with a code. Codes were then organized within a coding framework, which had been established before coding started and was refined during the coding process. Two coders were involved in the coding of the transcripts, and interrater agreement (IRA) was evaluated to be maintained above ≥ 0.7.

Qualitative research methods were used to determine the most salient concepts based on the number of patients who experience each and the average peak bother reported. Concepts were considered salient if they were reported by ≥ 5 patients (i.e., ≥ 5 patients report ever experiencing the concept regardless of whether it was experienced in the past, current, or both) and the average peak bother rating for the concept was ≥ 5. The average peak bother represents the average of the highest reported bother rating from each patient regardless of time point (i.e., if the bother rating was reported in the past or current). Due to the open-ended, semi-structured nature of the interviews, patients did not necessarily rate every concept that they reported. Additionally, not every concept was discussed with every patient, as some concepts did not arise until later waves (Additional file 1: Tables S4 and S5). Patients who did not provide a peak bother rating were not included in any of the average peak bother rating calculations and also not factored into determining the number of patients ever experiencing each concept. The data from the patient interviews was synthesized to develop the final conceptual model of WD. Data were also analyzed to explore the change in the patient experience over time and to evaluate potential subgroups of patients based on symptoms reported.

A post hoc analysis was conducted to ensure that comorbidities did not substantially influence the concepts being identified as important to WD. To achieve this, patients with comorbidities were removed (one at a time) from the analysis of salient concepts, and the changes in number of mentions and/or bother ratings was assessed.

RESULTS AND DISCUSSIONS

TARGET LITERATURE REVIEWS

The TLR identified 569 articles of which 30 were includ. From these 30 articles, 35 concepts (25 signs/symptoms and 10 impacts) associated with WD were identified for inclusion in the preliminary conceptual model. Priority concepts (those where the upper prevalence range was ≥ 50% in the reviewed articles) included both neurological (such as slurred speech/speech disturbances, gait abnormalities, parkinsonism, tremors) and psychiatric (such as increased irritability/anger outburst, disinhibition) symptoms but no hepatic symptoms. Only one impact (catatonic/abnormal movement) also met the criteria for a prioritized concept. All concepts retrieved from the literature review were included in the preliminary WD conceptual model, with prioritized concepts in bold.

CLINICIANS INTERVIEWS

The clinicians interviewed were leading experts in the study of Wilson Disease (WD), had between 12 and 32 years of clinical experience, and were currently practicing in academic medical centers. Each

clinician had a different clinical subspecialty that aligned with the 3 core symptom categories (neurological, psychiatric, and hepatic).

Clinicians broadly agreed with the preliminary conceptual model. Ten of the signs/symptoms from the preliminary conceptual model were confirmed by clinicians as relevant to the patient experience and were maintained in the updated model with no changes to the wording as they were considered appropriately patient-friendly. These 10 signs/symptoms were tremor, headache, difficulty swallowing, yellow skin (jaundice), tendency to bleed easily, seizures, vomiting, fainting, joint pain, and joint stiffness. Table 1 describes changes made to signs and symptoms following clinician interviews. Clinicians recommended that the wording of 18 of the remaining signs/symptoms be revised to be made more patient- friendly; the language was amended with guidance from an experienced interviewer and qualitative researcher. Three signs and symptoms were removed from the conceptual model because they were considered to be treatment-related or not associated with the natural history of Wilson Disease (WD). Clinicians considered 6 additional symptoms identified through social media listening as relevant and proposed to include them in the conceptual model. In addition, clinicians mentioned 2 new signs/symptoms that were also added to the model.

Table 1 also describes changes made to impact of Wilson Disease (WD) on daily patient life in the model following clinician inter- views. Overall, the wording for 7 impacts was revised to render them more patient-friendly, 5 were excluded from the revised interim conceptual model because they were not considered relevant to the WD patient experience, and 6 new impacts were added. The interim conceptual model includes 45 signs/symptoms and 14 impacts.

Table 1 Changes based on clinician interviews

Signs/symptoms modified		**Impacts modified**	
Changes to existing symptoms		**Changes to existing impacts**	
Preliminary model	**Revised**	**Preliminary model**	**Revised**
Gait abnormalities	Changes in walking	Planning difficulties	Difficulty planning
Salivation	Drooling	Suicide attempts	Intentional self-harm
Bipolar disorder/mania	Mania	Self-injurious behavior	
Cognitive impairment	Changes in thinking skills (e.g., feeling slowed down, forgetful)	Catatonic/abnormal movement	Abnormal body movements
Attention deficit	Changes in attention (e.g., trouble focusing, easily distracted)	Limitations in function/daily activities	Limitations in physical function
Emotional lability	Frequent "ups and downs" in mood	Increased irritability/anger outburst	Anger outburst
Increased irritability	Irritability	Sleep disturbances/excessive daytime	Sleep disturbances
Apathy	Apathy (e.g., feeling disengaged, feeling like you do not care about anything anymore)	Spider	
Hyperactivity	Hyperactivity (e.g., cannot sit still, restless)		
Psychosis	Psychotic episode (e.g., hearing voicesthat no one else hears, seeing things that are not really there)		
Abdominal pain	Stomach pain		

veins Spide rveins (i.e.,

	small, damaged veinsvisible on the surface of the legs or face)	sleeping	Excessive daytime sleeping
Frailty	Frail (e.g., fragile, physically vulnerable / weak)		
Fatigue	Fatigue (e.g., extreme tiredness, low energy levels)		
Swelling	Swelling/fluid retention		
Slurred speech/speech disturbances	Slurred speech		
	Other changes in speech (e.g., vocal tremor, stuttering, slow speech)		
Parkinsonism	Changes in balance Changes in facial expression		
Dysexecutive syndrome	Difficulty solving problems Difficulty with decision making		

Symptoms removed	Impacts removed
Hair loss	Catatonia
Dry skin	Anger outbursts
Hypertension	Sudden physical collapse following strong emotion
	Dementia
	Anorexia
Symptoms added	**Impacts added**
Night sweats	Difficulty writing
Dizziness	Inability to walk/wheelchair bound
Shortness of breath	Change in work performance
Anaemia	Change in school performance
Enlarged/swollen liver	Impact on family life
Numbness in jaw	Impact on social life
Vertigo	
Kayser–Fleischer rings (greenish brown or golden rings around your eyes)	

Patients CE Interviews

Patient sample demographics and clinical history

Between May 2023 and June 2023, CE interviews were conducted with 11 patients with WD from the Lahore (n = 8) and Multan (n = 3). All but one patient was female (n = 10), and patients ranged in age from 18 to 65 years (mean = 38.9). Patients were diagnosed with WD between 5 and 55 years ago. Over the course of their disease history, these patients receive a variety of treatments, both prescription and non-prescription. All patients reported having adhered to a low Cu diet at some point during their diagnostic history. All patients were receiving treatment, whether prescription or dietary, at the time of the interview.

Patient and caregiver experience of WD

During the patient interviews, 74 signs/symptoms and 23 impacts were included for discussion.

Signs and symptoms: Across patient interviews, 63 different signs/symptoms were reported. Of these, 31 were considered hepatic, 19 neurological and 13 psychiatric. Patients reported an average of 24 different signs/symptoms over the course of their WD and specified experiencing an average of 21 signs/symptoms at the time of the interviews.

All but 3 symptoms were mentioned by patients in Wave 1 (n = 4) or Wave 2 (n = 4; Additional file. Of the 3 additional symptoms, vertigo and slurred speech were reported by the first patient in Wave

3 (n = 3), and fainting was mentioned by the second patient in Wave 3. As only 3 new concepts were described in Wave 3, and the last interviewed patient did not raise any new concepts, it was concluded that saturation for signs/symptoms was adequate.

Several hepatic (6), neurological (6), and psychiatric (11) signs and symptoms were considered salient (defined as ≥ 5 people ever experiencing a concept and the average peak bother rating ≥ 5). Among hepatic signs/symptoms, fatigue and nausea were the most commonly reported by patients, and both were considered highly bothersome (average peak bother ratings of 8.5 and 8.0, respectively). Other salient hepatic symptoms included stomach pain (8), frail (7.7), joint pain (9), stomach discomfort (6.2), muscle cramping (7), vomiting (8), stomach bloating (7.5), loss of appetite (7.6), and acid reflux (6.6).

Hepatic symptoms featured prominently in patients' description of their disease:

"I feel like I have phases where I'm good and I'm ready to go. Then sometimes I'm like I'm just so tired, hold on to things (Patient 5)".

"So, walking gets difficult because of changes in balance. So, my gait pattern changes because of that (Patient 5)".

"Dragging my feet mostly. Dragging my feet, and then sometimes, I'll just try and take a step and then it feels almost like I'm dizzy and I have to catch myself (Patient 6)".

"*I kind of sway back and forth sometimes walking… Like I can't walk in a straight line (Patient 9)".*

"I feel like have nothing…even though I have a full night of sleep (Patient 4)."

"I'm always tired. It's one of those things where you wake up in the morning and you think you're going to be rejuvenated from the night before if you sleep. I do have trouble sleeping, also. I'm just tired. I could sit down, but I can't…Kind of like somebody hit me with a truck (Patient 7)."

"I was constantly nauseous. I rarely vomited, but me and food did not get along (Patient 9)."

"[Nausea] that was a full-blown 10+…I couldn't even get up in the mornings (Patient 10)."

Patients detailed their experience of how WD was associated with a variety of psychiatric symptoms:

"I am very irritated easily. The littlest things just set me off. I get frustrated and impatient…I would say 9–10 because typically I'm a really relaxed calm easy-going person (Patient 1)."

"I've always had mood swings, but they weren't really pronounced. I noticed them, but other people never noticed them (Patient 9)."

"It's [anxiety] pretty much my whole life. Within the past few years it's been more than ever (Patient 11)."

Patients described in detail the varied and profound effect that WD symptoms had on their daily lives and HRQoL:

"Well, like I had mentioned I'm scared to the point where if I do ever have to have a liver transplant because having surgery, and having to be on a liver transplant list, and things like that, that's scary (Patient 1)."

"When I was diagnosed, it was like, don't play with XXX, she's got a disease. Don't go near XXX, you'll capture it (Patient 2)."

"A lot to do with being tired and pain. So, I think I have a lot of physical limitations consistently. So, I'd give that a 6 (Patient 6)."

"And, my social life too. I feel like I'm going to sit there and nod out. Can I go out to dinner? Once in a while. Can I drink? Previously, obviously. Go to a friend's house and there I am sitting in a chair and sleeping, because I'm just so exhausted (Patient 7)."

"…I got to the point where I would fall asleep in class. My teacher would wake me up. I would go to the next class. I would fall asleep and so forth until the rest of the day, and then I'd get home I could fall asleep (Patient 8)."

"It actually took me eight years to get my degree because of my fatigue mostly (Patient 11)."

"I wonder if I can ever have a full-time career… So I often worry about what I can do with my life (Patient 11)."

Patient experience with comorbidities

Comorbidities (Table 3) were not found to have a substantial impact on the WD patient experience. The same concepts were elicited by patients with and without comorbidities but there were some differences in salience when patients with comorbidities were removed one at a time from the analysis. Specifically, certain neurological (other changes in speech, tremor, change in writing and dizziness), hepatic (vomiting, stomach bloating and acid reflux), and psychiatric symptoms (apathy and frequent up and down in mood) were less salient when patients with comorbidities were removed from the over- all analysis of salient symptoms. In contrast, other symptoms such as night terrors/vivid dreams (psychiatric) and weight loss (hepatic) became relatively more salient when patients with comorbidities were removed from the sample. The only difference with respect to impacts was that feeling embarrassed, worried about how they are perceived by others, impact on family life and difficult writing became less salient.

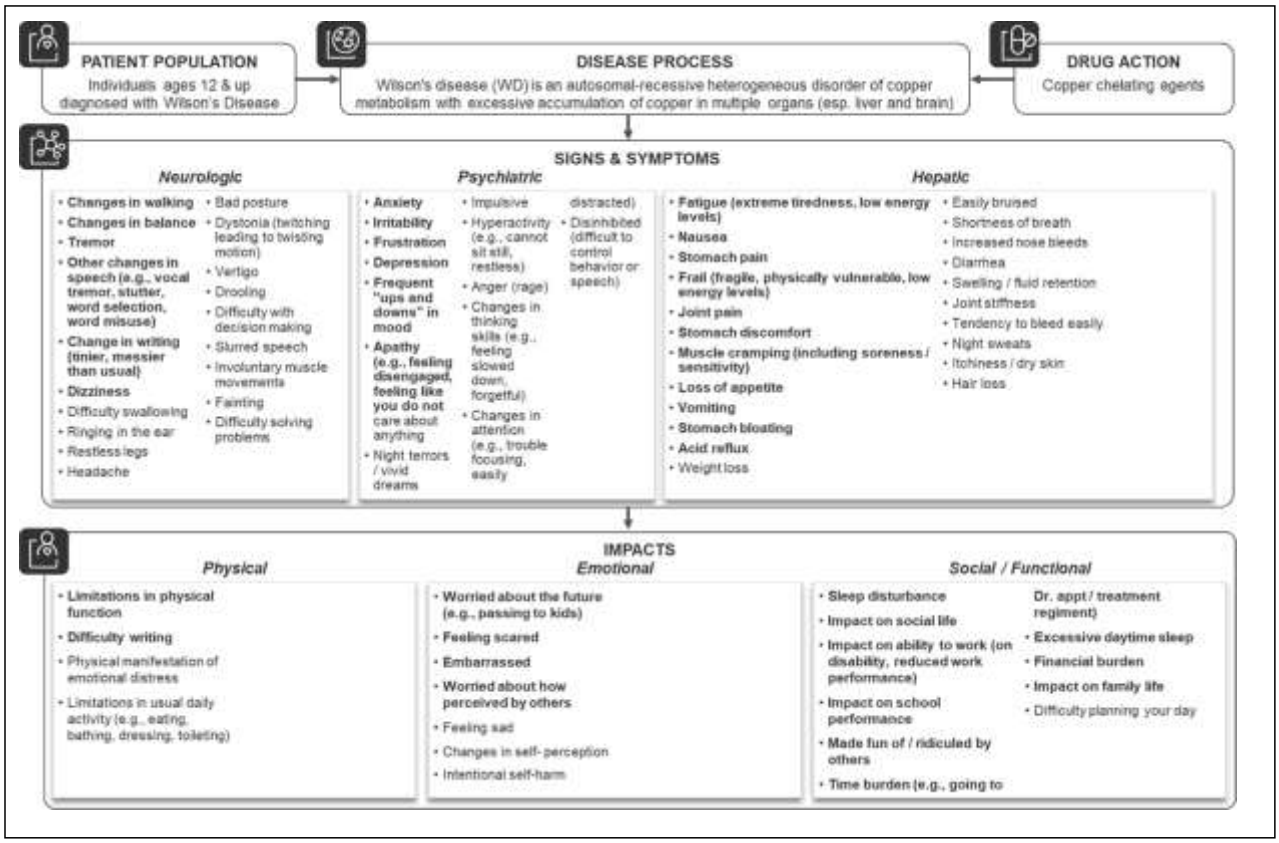
Final conceptual model

The final conceptual model includes 54 symptoms (22 hepatic, 19 neurological, 13 psychiatric) and 21 impacts with salient concepts depicted in bold.

Twenty of the 74 symptoms discussed with patients were excluded from the final conceptual model because they were not endorsed by patients (unable to walk/ unable to talk, difficulty eating, numbness in jaw, lower extremity pain related to swelling, skin rash, blurred vision), they would unlikely change with treatment in a clinical trial (changes in facial expression, asymmetry of face, stunted growth, spider veins), or they would not be easily captured through PRO measures (seizures, psychotic episode, mania, enlarged/swollen liver, anemia, portal vein hypertension, yellow skin [jaundice], green brown/gold rings around the eyes). In addition, joint swelling was removed due to low number of mentions and light sensitivity was removed because it was raised in the context of reactivity of the patient's blue eyes to light (e.g., during routine eye exams) and was not considered related to the disease.

Although hair loss and dry skin had previously been excluded from the interim conceptual model based on clinician interviews, patients mentioned these symptoms and considered them at least partly related to the disease. Itchiness and dry skin were merged into a single concept (itchiness/dry skin) and were included in the final model. Of the 23 impacts discussed with patients, the final model excluded inability to walk/wheelchair bound, and alcohol/abuse because they were not reported by patients in the interviews. Impacts were reorganized from immediate and general categories into 3 conceptual categories to better reflect feedback from interviews: physical, emotional and social/functional.

Fig 3. Final Conceptual Model



CONCLUSIONS

This work establishes a new understanding of what really matters to patients who experience symptoms of WD and how burdensome the different aspects of their condition can be over the course of their journey with this disease. It demonstrates that the hepatic symptoms experienced by many patients disrupt their lives and should be considered when treating these patients. Additionally, it defines subgroups of patients (those with hepatic as well as neurological and psychiatric signs/symptoms, and those without neurological signs/symptoms) that may be key for generating productive dialogue with each group of patients in clinical practice as well as for developing successful therapies for these 2 groups through clinical trials.

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