

Health-related quality of life in patients living with Wilson disease in Spain: a cross-sectional observational study

Zoe Mariño^{1*}, Marina Berenguer², Luis Peña-Quintana^{3,4}, Antonio Olveira⁵, Anna Miralpeix¹, Isabel Sastre², Ana Reyes-Domínguez³, Pilar Castillo⁵, Clàudia García-Solà¹, Ariadna Bono², Miriam Romero⁵, Francisco Javier Pérez-Sádaba⁶, Susana Aceituno⁶, Anna Anguera⁷

¹ Liver Unit, Hospital Clínic Barcelona, IDIBAPS, CIBERehd, ERN-RARE Liver, University of Barcelona, Barcelona, Spain; ZMARINO@clinic.cat (Z.M.); AMIRALPEIX@clinic.cat (A.M.); CLGARCIAS@clinic.cat (C.G-S.)

² Department of Gastroenterology and Hepatology, Hospital Universitari i polític La Fe, CIBERehd and IISLaFe, Valencia, Spain; marina.berenguer@uv.es (M.B.); isa.sastre99@gmail.com (I.S.); ariadna_bono@iislafe.es (A.B.)

³ Pediatric Gastroenterology, Hepatology and Nutrition Unit, Complejo Hospitalario Universitario Insular Materno-Infantil, Las Palmas de Gran Canaria, Spain; luis.pena@ulpgc.es (L.P-Q.); anitard71@gmail.com (A.R-D.)

⁴ ACIP. CIBEROBN, Instituto de Salud Carlos III, University of Las Palmas de Gran Canaria, Spain; luis.pena@ulpgc.es (L.P-Q.)

⁵ Department of Gastroenterology, Hospital La Paz, Madrid, Spain; aolveiram@gmail.com (A.O.); pcastillograu@gmail.com (P.C.); miriam.romero.portales@gmail.com (M.R.)

⁶ Outcomes'10 SLU, Castellón de la Plana, Spain; fperez@outcomes10.com (F.J.P-S.); saceituno@outcomes10.com (S.A.)

⁷ Medical Department, Alexion, AstraZeneca Rare Diseases, Spain; Anna.Anguera@alexion.com (A.A.)

* Correspondence: ZMARINO@clinic.cat

Research variables and instruments

- Unified Wilson's Disease Rating Scale consists of three subscales representing three main features of clinical manifestation in neurological WD: UWDRS I (1 item), UWDRS II (14 items), UWDRS III (19 items). Each item is scored on a five-point scale (0 points "no symptoms" and 4 points "worst characteristic possible") except for the first item, in which the maximum score is 3 points.
- The EuroQoL-5D-5L evaluates five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels of severity, corresponding to: 1) no problems, 2) slight problems, 3) moderate problems, 4) severe problems, and 5) extreme

problems. EQ-VAS ranging from 0 “worst possible” to 10 “best possible” health.

- The *ad hoc* questionnaire to evaluate the impact of WD on the patient’s life included questions ranging from 1) “not at all difficult” to 5) “extremely difficult” for questions about activities of daily living and from 1) “never” to 5) “all the time” for the rest of questions.
- SMAQ consists of six questions that evaluate different aspects of patient compliance with treatment: forgetfulness, routine, adverse effects, and quantification of omissions. A patient is classified as non-adherent if they respond to any of the questions with a non-adherence answer or if the patient has lost more than two doses during the last week or has not taken medication during more than two complete days during the last three months.
- WPAI consists of six questions related to the numbers of hours missed from work and usual activities, providing scores expressed as percentages for absenteeism, presenteeism, overall work impairment, and impairment of general activity. Using a scale from 0) “no effect” to 10) “health issues completely prevented me from doing work”.
- The CIQ comprises three questions about hours missed from class because of health issues, class hours attended, and how much health issues affected classroom productivity while attending classes. Using a scale from 0) “no effect” to 10) “health issues completely prevented me from doing work”.

Ad-hoc questionnaire

WD impact on patient's life (ADL, social, emotional, and executive function)

Activities of daily living impacts

| | Not at all difficult | A little bit difficult | Somewhat difficult | Very difficult | Extremely difficult |
|---------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Getting ready in the morning | <input type="checkbox"/> |
| Swallowing foods and/or liquids | <input type="checkbox"/> |
| Running errands | <input type="checkbox"/> |
| Doing housework or chores | <input type="checkbox"/> |
| Going to work | <input type="checkbox"/> |
| Physical activity or exercise | <input type="checkbox"/> |
| Sleeping | <input type="checkbox"/> |

Emotional impacts

| | Never | Rarely | Occasionally | Most of the time | All of the time |
|-----------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Feeling sad or depressed | <input type="checkbox"/> |
| Feeling anxious or worried | <input type="checkbox"/> |
| Feeling frustrated | <input type="checkbox"/> |
| Feeling angry | <input type="checkbox"/> |
| Feeling dependent on others | <input type="checkbox"/> |

Social impacts

| | Never | Rarely | Occasionally | Most of the time | All of the time |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Avoid spending time with other people | <input type="checkbox"/> |
| Avoid conversations with others | <input type="checkbox"/> |
| Difficulty making friends | <input type="checkbox"/> |
| Difficulty with my family | <input type="checkbox"/> |
| Trouble dating | <input type="checkbox"/> |
| Receiving unwanted attention from strangers | <input type="checkbox"/> |
| Relying on family for help | <input type="checkbox"/> |

Executive function impacts

| | Never | Rarely | Occasion- ally | Most of the time | All of the time |
|---|--------------------------|--------------------------|---------------------------|-----------------------------|----------------------------|
| Difficulty planning | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Difficulty remem- bering instructions | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Difficulty juggling multiple tasks | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Difficulty moving from one activity or situation to an- other | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Difficulty inde- pendently begin- ning an activity, generating ideas, and solving prob- lems | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Satisfaction, adherence & preferences regarding treatment *ad hoc* questionnaire (satisfaction questions adapted from TSQM)

SATISFACTION WITH WD TREATMENT:

- How satisfied are you overall with your current WD treatment?

| | | | | |
|---------------------|-------------|-------------|-----------|-------------------|
| Totally unsatisfied | Unsatisfied | Indifferent | Satisfied | Totally satisfied |
|---------------------|-------------|-------------|-----------|-------------------|

As a result of taking medication, do you experience any side effects? YES NO

- If ***YES***, rate your satisfaction with the treatment side effects experienced during treatment?

| | | | | |
|---------------------|-------------|-------------|-----------|-------------------|
| Totally unsatisfied | Unsatisfied | Indifferent | Satisfied | Totally satisfied |
|---------------------|-------------|-------------|-----------|-------------------|

ADHERENCE TO WD TREATMENT:

- How easy or difficult is it to follow the treatment you receive currently?

| | | | | |
|----------------|-----------|---------------|------|-----------|
| Very difficult | Difficult | Somewhat easy | Easy | Very easy |
|----------------|-----------|---------------|------|-----------|

- Do you ever forget to take your medication? YES NO
- Do you ever decide not to take your medication? YES NO
- During the last week, how many times did you fail to take your medication as prescribed? Never 1-2 times more than twice

PREFERENCES REGARDING WD TREATMENT:

Please indicate how strongly you agree with the following statements:

- I believe the treatment I receive is safe: Strongly agree/agree/disagree/strongly disagree/NA.
- I consider it necessary to monitor the copper levels through labs and another tests: Strongly agree/agree/disagree/strongly disagree/NA.
- Controlling my copper levels is a major burden on my daily life: Strongly agree/agree/disagree/strongly disagree/NA.
- I know how to take my medication correctly: Strongly agree/agree/disagree/strongly disagree/NA.

- My medication regimen is difficult to comply with: Strongly agree/agree/disagree/strongly disagree/NA.
- I needed to stop treatment due to side effects: Strongly agree/agree/disagree/strongly disagree/NA.
- I take too many pills daily: Strongly agree/agree/disagree/strongly disagree/NA.
- If I could, I would take fewer pills daily: Strongly agree/agree/disagree/strongly disagree/NA.

Figure S1. Frequency of concomitant treatment in patients with WD. *The group of “other medicines” was related to hormone drugs or vitamin supplements. One patient could be treated with more than one concomitant treatment.

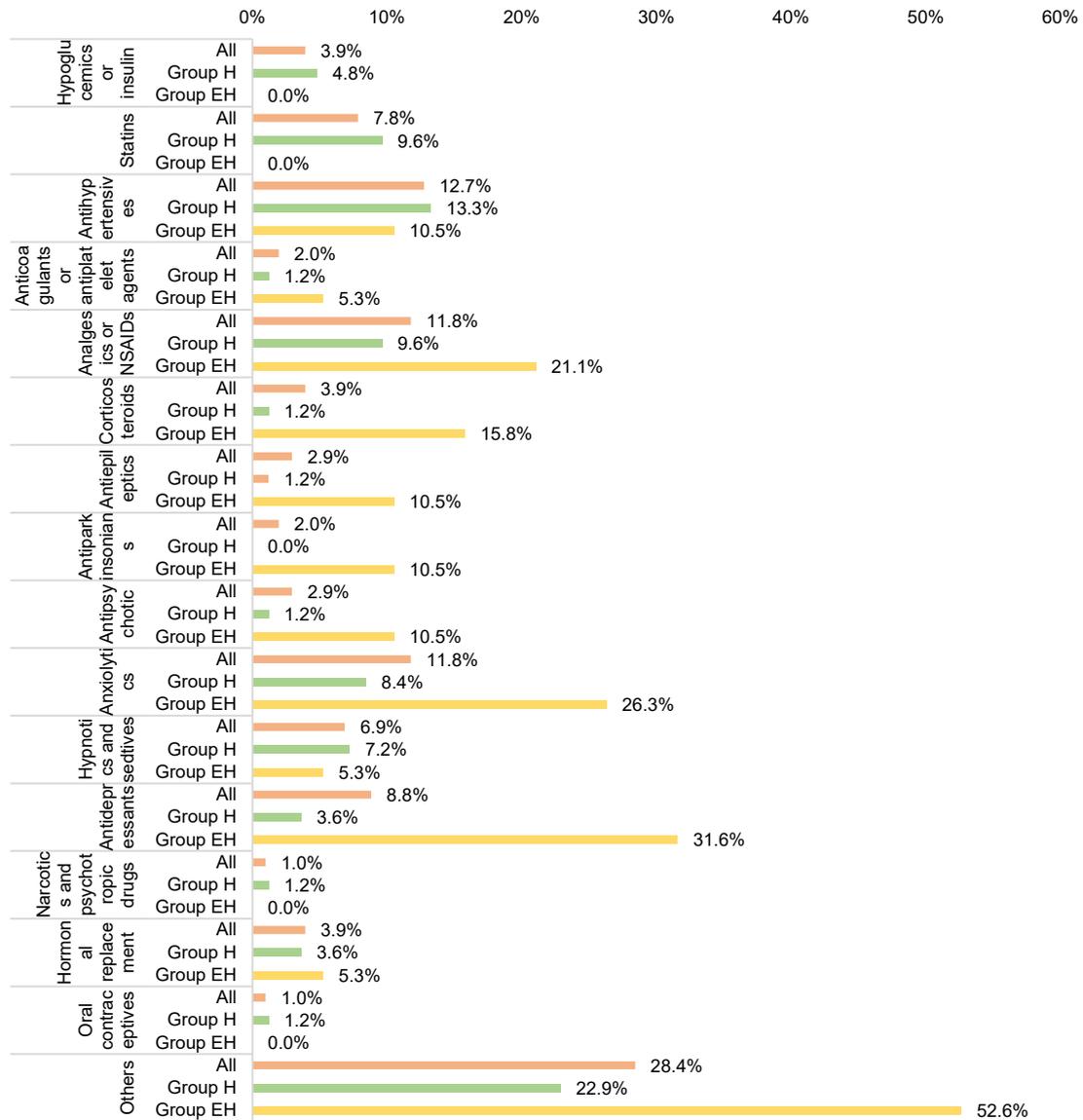


Figure S2. Frequency of the degree of agreement with the items in the preference questionnaire

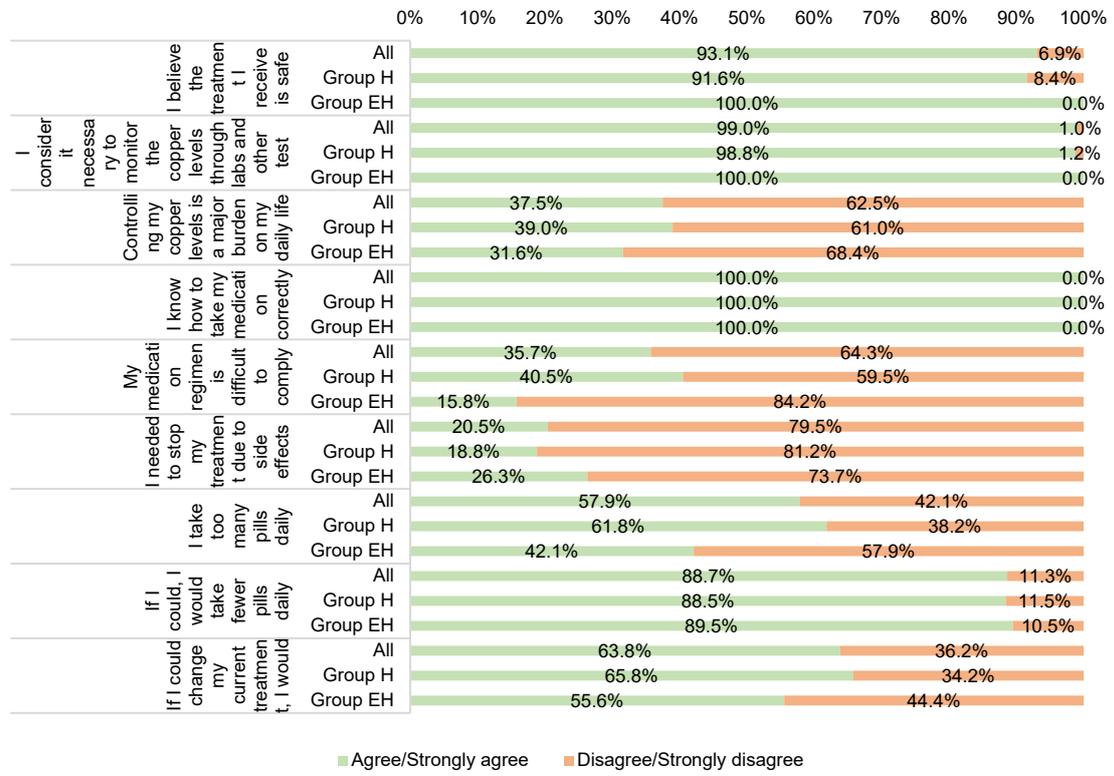


Table S1. Frequency of first treatment in all patients and by subgroup.

| First WD treatment | All | Group H | Group EH |
|--------------------------------------|-------------|----------------|-----------------|
| D-penicillamine, n (%) | 59 (57.8) | 46 (55.4) | 13 (68.4) |
| D-penicillamine + Zinc, n (%) | 7 (6.9) | 5 (6.0) | 2 (10.5) |
| Trientine, n (%) | 1 (1.0) | 0 (0.0) | 1 (5.3) |
| Trientine + Zinc, n (%) | 2 (2.0) | 1 (1.2) | 1 (5.3) |
| Zinc, n (%) | 32 (31.4) | 30 (36.1) | 2 (10.5) |
| Others*, n (%) | 1 (1.0) | 1 (1.2) | 0 (0.0) |
| Total, N (%) | 102 (100.0) | 83 (100.0) | 19 (100.0) |

EH: mixed or neurological involvement; H: isolated liver involvement. * Bis-choline tetrathiomolybdate.

Table S2. Evaluation of physician-determined and self-reported treatment adherence

| | All | | Group H | | Group EH | |
|--|--------------|--------------|--------------|--------------|--------------|--------------|
| | Yes | No | Yes | No | Yes | No |
| | N (%) |
| SMAQ | | | | | | |
| Have you ever forgotten to take your medication? | 70 (68.6) | 32 (31.4) | 61 (73.5) | 22 (26.5) | 9 (47.4) | 10 (52.6) |
| Do you always take your medication at the appropriate time? | 55 (53.9) | 47 (46.1) | 41 (49.4) | 42 (50.6) | 14 (73.7) | 5 (26.3) |
| When you feel bad, have you ever discontinued taking your medication? | 13 (12.7) | 89 (87.3) | 11 (13.3) | 72 (86.7) | 2 (10.5) | 17 (89.5) |
| Have you ever forgotten to take your medication during the weekend? | 20 (19.6) | 82 (80.4) | 19 (22.9) | 64 (77.1) | 1 (5.3) | 18 (94.7) |
| Self-reported | | | | | | |
| Have you ever forgotten to take your medication? | 69 (67.6) | 33 (32.4) | 60 (72.3) | 23 (27.7) | 9 (47.4) | 10 (52.6) |
| Do you forget to take your medication over the weekend? | 25 (24.5) | 77 (75.5) | 21 (25.3) | 62 (74.7) | 4 (21.1) | 15 (78.9) |
| Do you ever voluntarily decide not to take your medication? | 12 (11.8) | 90 (88.2) | 8 (9.6) | 75 (90.4) | 4 (21.1) | 15 (78.9) |
| Did you always take your medication during the last week? | 61 (59.8) | 41 (40.2) | 47 (56.6) | 36 (43.4) | 14 (73.7) | 5 (26.3) |
| Did you fail to take your medication once or twice during the last week? | 34 (33.3) | 68 (66.7) | 31 (37.3) | 52 (62.7) | 3 (15.8) | 16 (84.2) |
| Did you fail to take your medication more than twice during the last week? | 7 (6.9) | 95 (93.1) | 5 (6.0) | 78 (94.0) | 2 (10.5) | 17 (89.5) |

EH: mixed or neurological involvement; H: isolated liver involvement; SMAQ: Simplified Medication Adherence Questionnaire

Table S3. Productivity evaluation according to the Work Productivity and Activity Impairment questionnaire

| | All | | Group H | | Group EH | |
|---|-------------|-----|-------------|----|-------------|----|
| | Mean % (SD) | n | Mean % (SD) | n | Mean % (SD) | n |
| Percentage of work time missed due to the disease | 3.6 (0.2) | 51 | 3.1 (15.5) | 45 | 6.9 (10.8) | 6 |
| Percentage of how your illness affected your productivity while you were working | 6.7 (0.2) | 51 | 5.3 (17.0) | 45 | 16.7 (27.3) | 6 |
| Percentage of overall work impairment due to the disease | 7.8 (0.2) | 51 | 6.1 (17.9) | 45 | 20.4 (30.8) | 6 |
| Percentage of school time missed due to the disease | 1.5 (0.04) | 26 | 1.6 (4.4) | 24 | 0.0 (0.0) | 2 |
| Percentage of how your illness affected your productivity while being at school due to the disease | 5.4 (0.2) | 26 | 1.3 (3.4) | 24 | 55.0 (63.6) | 2 |
| Percentage of overall school impairment due to the disease | 6.9 (0.2) | 26 | 2.9 (5.2) | 24 | 55.0 (63.6) | 2 |
| Percentage of regular daily activity impairment due to the disease | 14.7 (0.3) | 102 | 9.0 (18.5) | 83 | 39.5 (40.6) | 19 |

EH: mixed or neurological involvement; H: isolated liver involvement; SD: standard deviation