Impact of Clinical and Sociodemographic Factors on Fatigue Among Patients With Substance Use Disorder: A Cohort Study From Norway for The Period 2016-2020

Jørn Henrik Vold (jorn.vold@uib.no)
Universitetet i Bergen Det medisinsk-odontologiske fakultet https://orcid.org/0000-0001-8701-7638
Rolf Gjestad
Haukeland University Hospital: Haukeland Universitetssjukehus
Christer F. Aas
Haukeland University Hospital: Haukeland Universitetssjukehus
Fatemeh Chalabianloo
Haukeland University Hospital: Haukeland Universitetssjukehus
Svetlana Skurtveit
FHI: Folkehelseinstituttet
Else-Marie Løberg
Haukeland University Hospital: Haukeland Universitetssjukehus
Kjell Arne Johansson
Haukeland University Hospital: Haukeland Universitetssjukehus
Lars Thore Fadnes
Haukeland University Hospital: Haukeland Universitetssjukehus

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Abstract

Background The impact of clinical and sociodemographic factors on fatigue remains unknown among patients with substance use disorders (SUD). This study aims to evaluate fatigue among patients with SUD using a nine-item fatigue severity scale (FSS-9) and identify the impact that clinical and sociodemographic factors – such as injecting substance use, chronic infectious diseases, liver fibrosis, opioid agonist therapy (OAT), debt difficulties, and housing situation – have on fatigue.

Methods We used data from a cohort of patients with SUD in Norway with annual health assessments surveying FSS-9 and some clinical and sociodemographic factors. A total of 915 FSS-9 measurements were collected from 654 patients during the period 2016-2020. We defined baseline as the first annual health assessment when the health assessments were listed chronologically. Time was defined as months from baseline. We used a linear mixed model to analyse whether the clinical and sociodemographic factors affected the FSS-9 sum score, presented with beta coefficients (β) with 95% confidence intervals (CI).

Results The mean sum score of the FSS-9 was 43 (standard deviation: 16) at baseline. Being female (change in FSS-9 sum score: 4.1, 95 % CI: 1.3-7.0), having debt difficulties (2.9;0.4-5.3), and using benzodiazepines (5.7;3.0-8.4), amphetamine or cocaine (-5.0;-8.0–2.0) affected the FSS-9 sum score. The other clinical and sociodemographic factors did not predict any clinically relevant change in the FSS-9 sum score from baseline to the following health assessments.

Conclusion Patients with SUD suffer from high levels of fatigue. Focusing on closer follow-up of females and reducing debt difficulties and the use of benzodiazepines may mitigate fatigue in the SUD population.

Intro-hcv Study Group Participating Investigators

Bergen: Christer Frode Aas, Vibeke Bråthen Buljovcic, Fatemeh Chalabianloo, Jan Tore Daltveit, Silvia Eiken Alpers, Lars T. Fadnes (principal investigator), Trude Fondenes Eriksen, Per Gundersen, Velinda Hille, Kristin Holmelid Håberg, Kjell Arne Johansson, Rafael Alexander Leiva, Siv-Elin Leirvåg Carlsen, Martine Lepsøy Bonnier, Lennart Lorås, Else-Marie Løberg, Mette Hegland Nordbotn, Cathrine Nygård, Maria Olsvold, Christian Ohldieck, Lillian Sivertsen, Hugo Torjussen, Jørn Henrik Vold, Jan-Magnus Økland

Stavanger: Tone Lise Eielsen, Nancy Laura Ortega Maldonado, Ewa Joanna Wilk

proLAR: Ronny Bjørnestad, Ole Jørgen Lygren, Marianne Cook Pierron

Oslo: Olav Dalgard, Håvard Midgard, Svetlana Skurtveit

Bristol: Peter Vickerman

1. Background

Patients with Substance Use Disorders (SUD) suffer from a broad range of health-related difficulties that may contribute to fatigue [1–3]. Fatigue presents itself as a persistent and overwhelming feeling of exhaustion and loss of energy. The condition is mainly associated with chronic diseases and may mitigate treatment adherence and exacerbate comorbid disorders [4, 5]. In SUD populations, a myriad of external factors can interact with fatigue and affect these patients' general well-being [6–8]. Injecting substance use, internal organ dysfunctions (predominantly kidney and liver diseases), mental disorders, as well as low income, unemployment, and homelessness are some of the external factors that interact with fatigue. Despite this, relatively little attention has been paid to the extent of fatigue and how much various external factors influence fatigue among patients with SUD. Therefore, understanding the key factors affecting fatigue is essential to improve treatment outcomes and adherence in this population.

Fatigue is associated with several sociodemographic and clinical factors. Among patients with the Hepatitis C Virus (HCV) infection, 50–80% have reported fatigue [9], while 33–88% of those with the Human Immunodeficiency Virus (HIV) infection have presented the same symptom [10]. A more uncertain prevalence of fatigue is seen among patients with the Hepatitis B Virus (HBV) [11, 12]. In addition, females, patients with lower educational levels, and those with opioid use disorders undergoing Opioid Agonist Therapy (OAT) with methadone or buprenorphine generally have a greater risk of fatigue [13, 14]. Disentangling the effects of the potential factors influencing fatigue in patients with SUD is essential for individualised treatment and developing clinical guidelines.

Fatigue is a subjective concept, and various definitions and instruments are used in the literature to capture it, which makes interpretations more complicated [15–17]. The nine-item fatigue severity scale (FSS-9) is a well-known questionnaire used to quantify fatigue treatment effects. It shows excellent validity and reliability across various chronic neurological and infectious diseases, such as multiple sclerosis [15], HCV infection [18], stroke [5], and Parkinson's disease [19]. The fact that FSS-9 shows a high consistency across various chronic diseases makes it particularly suitable to estimate fatigue among patients suffering from SUD with complex and challenging comorbidities.

Thus, this prospective cohort study aims to investigate fatigue using the nine-item Fatigue severity scale (FSS-9) among patients with substance use disorders (SUDs) and predict the impact of sociodemographic and clinical factors on FSS-9, including educational level, housing situation, debt difficulties, chronic infectious diseases, injecting substance use, substance use, liver fibrosis, and kidney disease. Moreover, we estimate:

1. using annual health assessments, the FSS-9 sum score and whether and to what extent the sociodemographic and clinical factors impact this score;
2. the impact of sociodemographic and clinical factors on changes in the FSS-9 sum score from the first health assessment to the following annual health assessments;
3. for patients on opioid agonist therapy (OAT) receiving methadone or buprenorphine, the FSS-9 sum score, whether and to what extent the sociodemographic and clinical factors affect the FSS-9 sum score at baseline, and any changes in the FSS-9 sum score from the first health assessment to the following annual health assessments.

2. Methods

2.1. Data source

We used data from a cohort nested to the INTRO-HCV trial on patients with SUD in Bergen and Stavanger, Norway [20]. We collected data from May 2016 to January 2020, and recruited patients on OAT from outpatient clinics in Bergen and Stavanger, as well as patients with various SUDs receiving primary healthcare from the municipality clinics in the city of Bergen.

2.2. Data collections

All included patients were assessed yearly with a health assessment, including FSS-9 measurements, sociodemographic data, and current substance use. Additionally, blood samples and liver fibrosis measurements using transient elastography were conducted. We collected all data in a health register using electronic data collection software (Checkware®) under research nurses' supervision. All the clinical data, including information regarding OAT, OAT medication, substance use, and possible comorbid clinical conditions, were collected from the electronic medical record.

2.3. Study population

We included 915 FSS-9 measurements from 654 patients in the study period. In total, 225 had follow-up data and conducted the health assessment, including the FSS-9 questionnaire, twice (n=188) or thrice (n=37), providing 487 repeated

measurements. The median interval between the health assessments, including FSS-9 measurements, was 11 months (Interquartile range (IQR): 9 – 14) (Additional File 1).

2.4. Measuring fatigue

We measured fatigue during the last week using FSS-9, including items considering: mental and physical functioning, motivation, carrying out duties, and interference with work, family, or social life. An FSS-9 measurement was completed when all nine items in the questionnaires were entirely conducted during an annual health assessment. The FSS-9 items were answered on a Likert scale – ranging from 1 (no fatigue) to 7 (worst fatigue) – that demonstrates the fatigue level. A high score of FSS-9 items notes a high level of fatigue, while a mean FSS-9 item score greater than 4.0 revealed severe fatigue. The data collection software only allowed valid responses to each question and prompted empty questions before submission to minimise missing data. The FSS-9 was also translated and back-translated from the US-English version into Norwegian by qualified native Norwegian-speaking translators (Additional File 2) [21].

2.5. Measuring liver stiffness and assessing blood samples

We assessed liver stiffness using transient elastography (Fibroscan®) to reveal liver fibrosis and cirrhosis. The elastography was reported as a median score of 10 measurements conducted by research nurses. A liver stiffness above 10 kilopascals (kPa) was defined as liver fibrosis, while a value above 12.5 kPa indicated liver cirrhosis [22]. We also collected blood samples, including hemoglobin, thrombocytes, C - reactive protein, aspartate aminotransferase, estimated glomerular filtration rate, hepatitis B surface antigen (HBsAg), HIV antigen/antibodies, HCV antibodies, and HCV polymerase chain reaction (HCV PCR) during the annual health assessment. Liver stiffness was estimated by calculating the AST to platelet ratio index (APRI) score and using transient elastography (Fibroscan®) (Additional File 3). Moreover, the hematological and biochemical samples were analysed to detect anemia (Hemoglobin), infection or inflammation (C – reactive protein), kidney disease (estimated glomerular filtration rate), liver disease (APRI), or chronic infectious diseases (HIV, HCV, and HBV), which could affect the FSS-9 score. Both elastography and blood samples were examined annually and simultaneously when conducting the annual health assessments. We analysed the blood samples at the Department of Laboratory Medicine, Haukeland University Hospital, Bergen, Norway, and at the Department of Medical Biochemistry and Microbiology, Stavanger University Hospital, Stavanger, Norway (accredited by ISO-standard 15189).

2.6. Definition of study variables, including sociodemographic and clinical factors

We defined baseline for patients as the first annual health assessment that included an FSS-9 measurement when we listed the health assessments chronologically. We dealt with each FSS-9 measurement as a sum score by summarising the value (one to seven) from each item and as a mean score calculated by dividing the sum score by nine (nine items). We defined being on OAT according to whether patients received buprenorphine or methadone (OAT opioids) at baseline. Further, in accordance with the World Health Organization's standards, we calculated the daily dose of received OAT opioids as a ratio between the received dose per day divided by the expected mean dose of OAT opioids (buprenorphine 18 mg, buprenorphine-naloxone 18/4.5 mg or methadone 90 mg) [23]. We categorised educational level into five groups: 'not completed primary school,' 'completed primary school (nine years),' 'completed high school (12 years),' 'three or fewer years of college or university' or 'more than three years of college or university.' Patients' housing situations in the 30 days prior to the FSS-9 measurement were classified into two groups: "stable" and "unstable." The latter category involved patients who had lived on the street, in a homeless shelter, or with family and friends during the past 30 days. Others who had a more permanent residence were classified as having a stable housing situation. Debt difficulties were defined as striving with paying off legal or illegal debt due to a constrained private economy. We set 'injecting substance use' as having injected at any time during the past 12 months, whereas frequent substance use was categorised as consuming at least one of the substance groups, including 'benzodiazepines or z-hypnotics,' 'cannabis,' 'stimulants (amphetamine or cocaine),' 'alcohol,' and 'heroin or other illicit opioids', more than weekly during the 12 months prior to a health assessment. Patients who did not use substances or used them less than weekly during the past 12 months were categorised as having 'no frequent use

of substance'. Having chronic infectious diseases was defined as detecting HCV PCR (HCV), HBsAg (HBV), or HIV antigen/antibodies (HIV) in the blood samples. For HCV PCR, we used the Helmert contrast in order to classify patients into two groups – transmitted and non-transmitted – and further into two subgroups: whether patients have a low viral load (< 800 000 IU/ml) or high viral load (≥ 800 000 IU/ml). A high virulent HCV infection indicates a high liver inflammation level and a greater likelihood of fatigue [24].

2.7. Statistical analyses

We used Stata/SE 16.0 (StataCorp, TX, USA) for descriptive analysis and IBM SPSS version 26.0 for expectation-maximisation imputation and linear mixed model analyses. The threshold for statistical significance was set to $P < 0.05$ for all analyses unless otherwise stated. In all analyses, we defined time as months from baseline.

We dealt with any missing values concerning sociodemographic and clinical factors – such as educational level, housing situation, debt difficulties, receiving OAT, OAT opioid dose ratio, injecting substance use, substance use, and the results of defined blood samples and transient elastography – as 'missing at random' when running expectation-maximisation imputation. We identified missing values in 2.6 % in these factors and all were replaced with estimated values by imputation.

The FSS-9 sum score at baseline was calculated by summarising the nine items' points. Linear mixed model analyses were used to investigate whether the sociodemographic and clinical factors affected the FSS-9 sum score and to what extent they impacted any changes in the score from baseline to following the health assessments. First, the factor variables were analysed separately as outcome variables as a function of the time (time from baseline). We did not identify substantial significant changes in the sociodemographic and clinical factors between the annual health assessments. Thus, baseline levels were used as stable predictors in the prediction of the level and changes in FSS-9. We specified the linear mixed models as a random intercept fixed slope regression model. The estimator was set to Restricted Maximum Likelihood. To explore whether predictors predicted changes in outcome, the interactions between these factors and time were added to the model. The full information maximum likelihood ensured that all available FSS-9 sum score measurements were used. Additionally, we ran similar analysis models by only including OAT patients using methadone or buprenorphine, respectively. For these analyses, we added the OAT opioid ratio as a predictor. The potential correlations between sociodemographic and clinical factors and fatigue are presented in Additional File 4.

2.8. Ethics approval and consent to participate

The study is reviewed and approved by the Regional Ethical Committee for Health Research West, Norway (REK Vest 2017/51). Each patient provided written informed consent prior to enrolling in the study.

3. Results

3.1. Patients characteristics at baseline

Seventy-one percent of patients were male, and the mean age was 43 years (standard deviation (SD): 11 years) at baseline (Table 1). Six percent had not completed primary school, or 44 % had primary school as their highest educational level. 82 % received OAT, of which 60 % received buprenorphine or buprenorphine-naloxone as an OAT opioid. Further, 13 % had an unstable housing situation in the last 30 days leading up to the FSS-9 measurement. 73 % had used at least one substance weekly during the past 12 months.

3.2.1 FSS-9 sum scores at baseline

The mean sum score for the FSS-9 was 43 (SD: 16), representing a mean score for the FSS-9 items of 4.8 (2.6) (Table 2). A total of 69 % of patients had severe fatigue. The mean FSS-9 sum score was slightly left-skewed (skewness: -0.7) and

tended towards a flattened distribution (kurtosis: 2.4).

3.2.2. The sociodemographic and clinical factors' impact on the FSS-9 sum score at baseline and the factors' influence on changes in the FSS-9 sum score from baseline to the following annual health assessments

At baseline, we found that the FSS-9 sum score was higher among female (FSS-9 sum score: 4.1, 95 % confidence interval: 1.3 to 7.0), patients with debt difficulties (2.9, 0.4 to 5.3) and those using benzodiazepines (5.7, 3.0 to 8.4), whereas the FSS-9 sum score was lower for patients using stimulants frequently (-5.0, -8.0 to -2.0) (Table 3). Further, using benzodiazepines frequently (-0.4, -0.7 to -0.1) and having liver fibrosis or cirrhosis measured by transient elastography (-0.5, -0.8 to -0.1) contributed a small non-clinical significant reduction of the FSS-9 sum score from baseline to the following annual health assessments.

3.2.3. The sociodemographic and clinical factors' impact on changes in the FSS-9 sum score from baseline to the following annual health assessments among patients on OAT

We did not find any differences in the FSS-9 sum score at baseline when comparing patients receiving methadone with patients using buprenorphine as an OAT opioid (Additional Files 5-6). However, among patients receiving methadone as an OAT opioid, we found that those being female (7.3, 2.5 to 12.2), having debt difficulties (4.9, 0.7 to 9.1), using benzodiazepines frequently (6.0, 1.6 to 10.5), and having a high HCV viral load (31.5, 1.5 to 61.5) increased the FSS-9 sum score at baseline. Among patients receiving buprenorphine as an OAT opioid, we found that using alcohol frequently (4.8, 0.2 to 9.3) increased the FSS-9 sum score, whereas using stimulants frequently (-5.0, -9.9 to -0.1) reduced the FSS-9 score at baseline. For both patients who received methadone or buprenorphine as OAT opioids, sociodemographic and clinical factors had no clinically relevant impact on changes in the FSS-9 sum score from baseline to the following annual health assessments.

4. Discussion

This study showed that 69% of SUD patients had severe fatigue symptoms. Fatigue was associated with being female, using benzodiazepines frequently, and having debt difficulties. In contrast, less fatigue was seen among patients using stimulant substances such as amphetamines. Comparing OAT patients receiving methadone with those using buprenorphine as an OAT opioid did not reveal any differences in fatigue. However, using benzodiazepines frequently, having debt difficulties, and having a high viral load of HCV were independently related to more fatigue among patients receiving methadone than those using buprenorphine.

In the present study, patients with SUD had a mean fatigue score (4.8) comparable to some of the most severe chronic diseases. In recent studies, patients infected with HIV or HCV, or those coinfected with both of them, had a mean FSS-9 score that ranged from 3.3 to 4.5 [25–27]. Patients with myasthenia gravis have reported a comparable fatigue score of 4.7 [28], and similarly, so have patients who have suffered from a stroke at least six months after the stroke onset (4.8) [29]. One can assume that a high prevalence of underlying mental disorders, extensive polysubstance use, and lower social status could have attributed to the high level of fatigue in the SUD population.

We found that females had higher levels of fatigue than males, mainly when benzodiazepines were used frequently. Recent studies evaluating fatigue in the general population and patients with chronic disorders have demonstrated similar gender differences in fatigue levels [13, 21, 28, 30]. Gender inequalities regarding household responsibilities and caring for the family have generally been highlighted as explanations for females' fatigue levels [31]. Additionally, females with SUD may be worse off than males in many domains. They may have less financial resources, experience more physical trauma caused by exchanging sex for drugs and money, and face more stigma related to family failures [31]. Moreover, in the general population and among patients with SUDs, females are more likely to use benzodiazepines than males, with a similar tendency found in different countries [2, 32–35]. Females' higher prevalence of anxiety disorders, sleeping disorders,

and the fact that they are more likely to seek medical care may contribute to more prescriptions of hypnotics and anxiolytics, such as benzodiazepines and z-hypnotics [36–38]. One can believe that these medical, psychological, and social challenges may overall explain the gender gap concerning a higher fatigue level among females in the SUD population.

Our findings reveal that frequent use of benzodiazepines increases fatigue, while frequent use of stimulants decreases fatigue. The impact of these substances on fatigue was expected considering benzodiazepines' sedative properties and the stimulating effects of amphetamines or cocaine. Nevertheless, the substances' impact was small, with an average FSS-9 sum score change of plus five points for benzodiazepine use and minus five points for stimulant use on a scale ranging from nine to 63 points. However, the associations between fatigue and substance use in SUD populations are not fully investigated. Benzodiazepine use is overall associated with lower quality of life, self-reported physical health, and more disability than non-benzodiazepine use in the general population [39, 40], which is transferable with the lower fatigue levels shown in the present study. Furthermore, using stimulants, particularly illicit amphetamines, is generally associated with poor mental health and stimulant withdrawal symptoms in the SUD populations [41, 42]. A temporary sense of better self-perceived mental health and fewer withdrawal symptoms may arise when consuming stimulant substances, which contributes to a temporary reduction of fatigue compared to the experience without stimulants. Therefore, FSS-9 scores could have reached a higher level for some stimulant users depending on the use of stimulants before health assessments, the frequency of use, and whether the cases involved underlying mental health conditions or ongoing withdrawal symptoms.

The present study shows no clear associations between fatigue and chronic infectious diseases or kidney disease. For the lack of association between HBV and fatigue among SUD patients, no comparable studies are presented; however, studies comparing patients with HBV in the general population and healthy controls show equivocal results when it comes to fatigue [11, 12]. For patients with HIV or end-stage kidney disease, the low prevalence of HIV and a mean renal function within the normal range could explain why no associations with fatigue were detected. Furthermore, we were surprised that patients with HCV infections did not demonstrate a higher fatigue level. However, the large extent of polysubstance use in the present population (75%) could have temporarily displaced the HCV infection's impact on fatigue.

We did not find any fatigue level differences when comparing patients using methadone with those using buprenorphine as an OAT opioid. However, we found that some sociodemographic and clinical factors affected fatigue among methadone users. Methadone is a full opioid agonist associated with more euphoria and analgesia than the partial opioid agonist buprenorphine [43]. In a quantitative study evaluating patients' experience of using methadone and buprenorphine on OAT, over-sedation has been particularly pointed out as a negative physical effect of methadone in some cases [44]. Therefore, there was some surprise that in the present study patients on methadone did not reach a higher fatigue level compared to patients using buprenorphine. Notably, according to Norwegian OAT guidelines, buprenorphine is the first drug of choice when entering OAT [45]. In line with the Norwegian recommendation, buprenorphine has been increasingly used in OAT during recent years [46]. Our results could indicate a high degree of similarity between methadone and buprenorphine users in terms of the degree of opioid dependence and sociodemographic and clinical factors, including substance use, which could contribute to the inability to identify fatigue differences.

5. Strengths And Limitations

This study has several strengths. We have included 654 patients with SUD that usually are difficult to reach in health care. Of those, 225 patients were followed up by two or three annual health assessments, making longitudinal analyses possible. This study does, however, have some limitations. First, the patients were mainly recruited from outpatient clinics receiving OAT. The majority had opioid dependence, although this was often combined with other dependencies, which could affect the generalisability of our results to other SUD populations. Second, we had a prospective follow-up of only a third of those patients recruited at baseline. This also causes weakness in our results and makes it necessary to carefully interpret the

longitudinal analyses. Third, due to clinical challenges, including systematic and patient delays, the annual health assessments were not precisely conducted one year after the previous health assessment. This may affect the interpretation of the predicted fatigue level changes from baseline.

6. Conclusion

The present study shows that patients with SUD suffer from substantial fatigue symptoms. We saw more fatigue symptoms among females, those who used benzodiazepines, and those with debt difficulties, while those using stimulants were slightly less fatigued. We did not identify any direct differences between the OAT medications methadone and buprenorphine. Still, methadone seemed to be an effect modifier potentiating more sociodemographic and clinical factors than buprenorphine. In conclusion, focusing on a closer follow-up of females, reducing debt difficulties, and helping patients minimise the extensive use of benzodiazepines may mitigate fatigue in the SUD population.

7. Abbreviations

APRI: Aspartate transaminase to platelet ratio index

CI: Confidence interval

FSS-9: Nine-item Fatigue Severity Scale

HBsAg: Hepatitis B surface antigen

HBV: Hepatitis B Virus

HCV: Hepatitis C Virus

HCV PCR: HCV polymerase chain reaction

HIV: Human Immunodeficiency Virus

IQR: Interquartile range

OAT: Opioid Agonist Therapy

SUD: Substance use disorder

SD: Standard deviation

8. Declarations

Ethics approval and consent to participate

The study has been reviewed and approved by the Regional Ethical Committee for Health Research (REC) West, Norway (reference number: 2017/51/REK Vest, dated 29.03.2017/20.04.2017). Each patient provided written informed consent prior to enrolling in the study.

Consent for publication

Participants have consented for publication

Availability of data and material

No additional data are available due to data protection requirements.

Competing interests

Not applicable

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Authors' contributions

Jørn Henrik Vold and Rolf Gjestad have led the study design, analysis, and article preparation. Christer Aas, Fatemeh Chalabianloo, Svetlana Skurtveit, Else-Marie Løberg, Kjell Arne Johansson, and Lars Thore Fadnes have contributed by leading the study design, analysis, and article preparation. All authors have read and approved the final article.

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Authors' information

Jørn Henrik Vold, MD, Department of Addiction Medicine, Haukeland University Hospital, and Department of Global Public Health and Primary Care, University of Bergen. Mailing address: Department of Addiction Medicine, Haukeland University Hospital, Jonas Lies vei 65, N-5021 Bergen, Norway. E-mail: jorn.vold@uib.no.

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Tables

Table 1
Sociodemographic and clinical characteristics at baseline for all patients and for patients with more than one annual health assessment

	All patients (N = 654)	Patients with > 1 health assessment (N = 225)
Age (years), n (%)		
18–29	81 (12)	23 (10)
30–39	185 (28)	63 (28)
40–49	205 (31)	75 (33)
50–59	148 (23)	53 (24)
≥ 60	35 (5)	11 (5)
Mean (SD)	43 (11)	44 (10)
Gender, n (%)		
Male	461 (71)	170 (76)
Female	193 (29)	55 (24)
Highest educational level, n (%)		
Not completed primary school	40 (6)	15 (7)
Completed primary school (9 years)	286 (44)	105 (47)
Completed high school (12 years)	259 (40)	81 (36)
≤ 3 years of college or university	57 (9)	20 (9)
> 3 years of college or university	12 (2)	4 (2)
Receiving opioid agonist therapy, n (%)	537 (82)	205 (91)
OAT opioid (%)		
Methadone	209 (39)	96 (43)
Buprenorphine/Buprenorphine-naloxone	321 (60)	107 (48)
OAT opioid dose ratio (median (IQR))[1)]	0.9 (0.8–1.1)	1.0 (0.9–1.1)
Housing situation the past 30 days, n (%)		

FSS-9: Nine-item Fatigue Severity Scale (Likert scale); HCV: Hepatitis C virus; HBsAg: hepatitis B surface antigen; IQR: Interquartile range; OAT: opioid agonist therapy; SD: Standard deviation.

[1)] OAT opioid ratio is a ratio between the received dose of OAT opioids per day and the expected median daily dose (18 mg buprenorphine or 18/4.5 mg buprenorphine-naloxone or 90 mg methadone). A ratio on 1.0 indicates that patients received an expected dose daily; [3)] A stable housing situation was defined as having owned or rented housing situation or being imprisoned; [4)] Unstable housing situation was defined as living in a homeless shelter, with family or friends, or on the street; [5)] Frequent substance use was defined as using substance at least weekly during the past 12 months.

The table displays the sociodemographic and clinical characteristics at baseline for the included patients, and for patients with two or more health assessment, including FSS-9 measurement during the study period.

	All patients (N = 654)	Patients with > 1 health assessment (N = 225)
Stable[3)]	569 (87)	203 (90)
Unstable[4)]	85 (13)	22 (10)
Injected substances the past 12 months, n (%)	338 (56)	116 (52)
Frequent substance use the past 12 months, n (%)[5)]		
Alcohol	154 (26)	56 (25)
Benzodiazepines	238 (39)	87 (39)
Cannabis	313 (52)	124 (55)
Opioids	97 (16)	27 (12)
Stimulants (amphetamines and cocaine)	176 (29)	60 (27)
Chronic infectious diseases, n (%)		
Hepatitis C virus infection	315 (48)	184 (82)
Low virulent (< 800 000 IE/ml)	168 (25)	92 (41)
High virulent (≥ 800 000 IE/ml)	147 (22)	92 (41)
Hepatitis B virus infection	5 (0)	< 5 (< 1)
Human immunodeficiency virus	< 5 (< 1)	< 5 (< 1)
Hematological and biochemical samples, median (IQR)		
Hemoglobin (g/dl)	14 (13–15)	14 (13–15)
Estimated glomerulus filtration rate (ml/min/1.73 m^2)	104 (89–122)	105 (91–124)
C-reactive protein (mg/L)	4 (1–9)	3 (1–8)
Aspartate transaminase (U/L)	31 (23–50)	40 (30–65)
Liver stiffness, median (IQR)		
Transient elastography (kPa)	5 (4–7)	6 (5–8)
Aspartate transaminase to platelets ratio index	0.3 (0.2–0.6)	0.4 (0.3–0.8)

FSS-9: Nine-item Fatigue Severity Scale (Likert scale); HCV: Hepatitis C virus; HBsAg: hepatitis B surface antigen; IQR: Interquartile range; OAT: opioid agonist therapy; SD: Standard deviation.

[1)] OAT opioid ratio is a ratio between the received dose of OAT opioids per day and the expected median daily dose (18 mg buprenorphine or 18/4.5 mg buprenorphine-naloxone or 90 mg methadone). A ratio on 1.0 indicates that patients received an expected dose daily; [3)] A stable housing situation was defined as having owned or rented housing situation or being imprisoned; [4)] Unstable housing situation was defined as living in a homeless shelter, with family or friends, or on the street; [5)] Frequent substance use was defined as using substance at least weekly during the past 12 months.

The table displays the sociodemographic and clinical characteristics at baseline for the included patients, and for patients with two or more health assessment, including FSS-9 measurement during the study period.

Table 2
Mean (Standard deviation (SD)) item scores for single items on FSS-9 at baseline and follow-up

	Baseline (N = 654)	*Follow-up (N = 225)*
FSS-9	5.4 (2.0)	5.6 (2.0)
I1: My motivation is lower when I am fatigued		
I2: Exercise brings on my fatigue	4.7 (2.1)	5.0 (2.1)
I3: I am easily fatigued	4.5 (2.1)	4.8 (2.1)
I4: Fatigue interferes with my physical functioning	4.9 (2.1)	5.6 (2.0)
I5: Fatigue causes frequent problems for me	4.4 (2.2)	4.5 (2.2)
I6: My fatigue prevents sustained physical functioning	4.6 (2.2)	4.4 (2.2)
I7: Fatigue interferes with carrying out certain duties and responsibilities	5.0 (2.1)	5.0 (2.1)
I8: Fatigue is among my three most disabling symptoms	4.6 (2.3)	4.8 (2.3)
I9: Fatigue interferes with my work, family, or social life	4.9 (2.2)	4.6 (2.3)
Mean score of all items	4.8 (1.8)	4.9 (1.7)
Sum score of all items	43.2 (15.9)	43.8 (15.2)

Follow-up: FSS-9 score on the last health assessment during the study period among patients with two or more annual health assessments; FSS-9: Nine-item Fatigue Severity Scale (Likert scale); I: Item; SD: Standard Deviation.

Table 3
Linear mixed model of fatigue (FSS-9) adjusted for sociodemographic and clinical factors (N = 654)

Fixed effects		
	Effect estimate	Time trend (per month)
	Estimate (95% CI)	Slope (95% CI)
FSS-9 sum score	42 (26–58)	0.3 (-1.9–2.5)
Female	*4.1 (1.3–7.0)*	0.0 (-0.4–0.3)
Age per 10 years[1)]	0.2 (-1.0–1.4)	0.0 (-0.2–0.1)
Educational level	-1.1 (-2.6–0.3)	0.0 (-0.2–0.1)
Unstable housing situation	0.0 (-3.7–3.7)	0.2 (-0.3–0.7)
Debt difficulties	*2.9 (0.4–5.3)*	0.0 (-0.3–0.3)
Injecting substance use	-0.1 (-2.9–2.7)	-0.1 (-0.4–0.3)
Frequent use of substances		
Benzodiazepines	*5.7 (3.0–8.4)*	*-0.4 (-0.7* – -0.1)
Alcohol	1.8 (-1.1–4.6)	0.0 (-0.3–0.4)
Cannabis	1.2 (-1.4–3.8)	0.2 (-0.1–0.4)
Opioids	3.3 (-0.3–6.9)	-0.4 (-0.9–0.1)
Stimulants[2)]	*-5.0 (-8.0– -2.0)*	0.2 (-0.2–0.5)
Chronic infectious diseases		
Hepatitis B virus infection	3.3 (-10.4–16.9)	-0.2 (-1.4–1.0)
Hepatitis C virus infection	3.0 (-5.4–11.4)	-0.1 (-1.6–1.7)
- Detected	-0.4 (-10.3–10.9)	-0.6 (-1.4–0.2)
- Low vs. high viral load		
HIV	-0.1 (-15.3–15.5)	1.1 (-0.6–2.7)

APRI: Aspartate transaminase to platelet ratio index; CI: Confidence interval; CRP: C-reactive protein; FSS-9: Nine-item Fatigue Severity Scale; eGFR: estimated glomerular filtration rate; HIV: Human Immunodeficiency virus; kPa: Kilopascal; OAT: Opioid Agonist Therapy.

[1)] Age per 10 years was centred according to mean age (43 years) in the study population at baseline. [2)] Included amphetamine or cocaine use. The educational level: highest level of education was coded 0–4 with 4 as the highest educational level. Unstable housing situation: living on the street, homeless shelter, or with family and friends at any time during the past 30 days prior to the health assessment. Debt difficulties: struggling with repaying current illegal and legal debt. Injecting substance use: Having injected substance during the past 12 months prior to the health assessment. Frequent use of substances: at least weekly during the past 12 months prior to the health assessment. Viral load of HCV: From − 0.5 to 0.5, where the range ≥ − 0.5 to < 0 represents the low viral load (HCV PCR < 800 000 IE/ml), and the range ≤ 0.5 to > 0 identifies the high viral load (HCV PCR ≥ 800 000 IE/ml). Zero (0) defined patients without HCV infection.

The table displays a linear mixed model analysis (Restricted Maximum Likelihood regression) evaluating sociodemographic and clinical factors' (predictors) impact on the FSS-9 sum score at baseline and the predictors' impact on changes in the FSS-9 sum score (time trend) per month from baseline.

Fixed effects		
Liver stiffness		
Transient elastography per 10 kPa	1.2 (-1.6–4.0)	*-0.5 (-0.8 – -0.1)*
APRI score per 1 unit	0.5 (-0.6–1.5)	0.1 (-0.1–0.3)
Hematologic and biochemical blood samples (continuous variables)		
Hemoglobin per 1 unit (g/dL)	-0.3 (-1.1–0.6)	0.0 (-0.1–0.1)
eGFR per 30 units (ml/min/1.73 m^2)	0.0 (-2.0–0.9)	0.0 (-0.2–0.2)
CRP per 10 units (ml/L)	-0.1 (-0.6–0.7)	0.0 (-0.1–0.1)

APRI: Aspartate transaminase to platelet ratio index; CI: Confidence interval; CRP: C-reactive protein; FSS-9: Nine-item Fatigue Severity Scale; eGFR: estimated glomerular filtration rate; HIV: Human Immunodeficiency virus; kPa: Kilopascal; OAT: Opioid Agonist Therapy.

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The table displays a linear mixed model analysis (Restricted Maximum Likelihood regression) evaluating sociodemographic and clinical factors' (predictors) impact on the FSS-9 sum score at baseline and the predictors' impact on changes in the FSS-9 sum score (time trend) per month from baseline.

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