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Research article

Frequency and burden of potentially treatable symptoms in glioma patients with stable disease

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ABSTRACT

Background & aims: Glioma patients experience a multitude of symptoms that negatively affect their health-related quality of life. Symptoms vary greatly across disease phases, and the patients' stable phase might be particularly suitable for assessing and treating symptoms. Identifying symptoms and patients' needs is a first step toward improving patient care. In glioma patients with stable disease, we assessed the frequency and burden of patient-reported symptoms, examined how these symptoms co-occur, and also determined whether patients would consider treatment to ameliorate specific symptoms.

Methods: In this retrospective study, patients rated the frequency and burden of seventeen symptoms on a seven-point Likert scale and stated whether they would consider treatment for these symptoms. Correlations between frequency, burden, and considering treatment were evaluated with Kendall's Tau correlation coefficients. Based on partial correlations between symptom frequencies we visualized the symptoms as a network.

Results: Fifty-two glioma patients with stable disease were included (31 WHO grade II/III, 21 WHO grade IV). The top five symptoms were fatigue, memory problems, reduced physical fitness, concentration problems, and drowsiness. Fatigue had the highest median frequency (4.5, interquartile range 2.5). Over half of the patients experienced three or more symptoms simultaneously and associations between all symptoms were depicted as a network. Overall, 35% of patients would consider treatment for at least one symptom. The wish to undergo symptom treatment correlated only moderately with symptom frequency and burden (range of correlations 0.24–0.57 and 0.28–0.61, respectively).

Conclusion: Glioma patients with stable disease experience multiple symptoms with a consequently high symptom burden. Despite the high prevalence of symptoms, the inclination for

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symptom management interventions was relatively low. The most frequent and burdensome symptoms and the way they are interrelated could serve as a roadmap for future research on symptom management in these patients.

1. Introduction

Gliomas are primary brain tumors, characterized by continuous and infiltrative growth, causing a broad range of symptoms heavily impacting patients' health-related quality of life (HRQoL) [1,2]. Median survival ranges from thirteen months for glioblastoma to fifteen years for WHO grade II oligodendroglioma [3–5]. After diagnosis and initial treatment, the patient is monitored for potential tumor growth with clinical assessments and MRI scans [6]. This phase, after treatment but before inevitable tumor progression, is considered to be the stable phase. In this phase patients still experience a broad range of symptoms, including fatigue, depression, emotional distress, and cognitive complaints [7–11]. Optimization of symptom management and thereby potentially improving HRQoL is an important goal in the care of glioma patients in this phase. To achieve this aim, however, we need to understand which symptoms are both most frequent and burdensome. In this study, we will therefore explore the prevalence and burden of symptoms experienced by glioma patients during stable disease and aim at understanding whether patients would seek treatment for these symptoms.

Symptoms that glioma patients experience vary greatly during the disease course [12]. Armstrong et al. studied the prevalence and severity of symptoms in patients with gliomas at different stages of the disease [10]. Fatigue, drowsiness, difficulty remembering, disturbed sleep and distress were reported most frequently at diagnosis, during treatment, and follow-up. Of the follow-up patients, 46% reported having at least three moderate-to-severe symptoms, compared to 39% of newly-diagnosed patients. There were no large differences in reported symptoms between patients with lower and higher-grade tumors [10]. A systematic review demonstrated that the prevalence of symptoms varies strongly between different phases of the disease [2]. For example, cognitive deficits were most prevalent during the diagnostic and end-of-life phases, whereas anorexia and diarrhea were primarily reported during systemic treatment and radiation therapy. Because of this variance in experienced symptoms between phases of the disease, it is important to investigate symptomatology in specific patient groups at a similar point in time.

The stable phase might be specifically suitable for assessing and treating symptoms since at diagnosis and during treatment patients need to focus on time- and energy-consuming medical procedures. Moreover, some treatment-related symptoms, such as nausea or hair loss, can be self-limiting, while other symptoms, such as depression, have an enduring impact on HRQoL during the stable phase [13].

Daily problems with a brain tumour

This questionnaire addresses specific symptoms. We would like to know how often you have experienced these symptoms, how burdensome these have been ***during the pas two weeks***, and if you would consider treatment for this symptom. Please answer the questions by circling the number that best reflects your situation.

Symptom	*How often in the past two weeks?*	*How burdensome is this in the past two weeks?*	*Would you consider treatment?*
Fatigue	(never) 1---2---3---4---5---6---7 (continuously)	(no burden) 1---2---3---4---5---6---7 (unbearable)	**yes / no**
Reduced physical fitness	(never) 1---2---3---4---5---6---7 (continuously)	(no burden) 1---2---3---4---5---6---7 (unbearable)	**yes / no**
Sleepiness during the day	(never) 1---2---3---4---5---6---7 (continuously)	(no burden) 1---2---3---4---5---6---7 (unbearable)	**yes / no**
Memory problems	(never) 1---2---3---4---5---6---7 (continuously)	(no burden) 1---2---3---4---5---6---7 (unbearable)	**yes / no**
Difficulty concentrating	(never) 1---2---3---4---5---6---7 (continuously)	(no burden) 1---2---3---4---5---6---7 (unbearable)	**yes / no**
Disturbed sleep	(never) 1---2---3---4---5---6---7 (continuously)	(no burden) 1---2---3---4---5---6---7 (unbearable)	**yes / no**
Stress	(never) 1---2---3---4---5---6---7 (continuously)	(no burden) 1---2---3---4---5---6---7 (unbearable)	**yes / no**
Irritability	(never) 1---2---3---4---5---6---7 (continuously)	(no burden) 1---2---3---4---5---6---7 (unbearable)	**yes / no**
Dry mouth	(never) 1---2---3---4---5---6---7 (continuously)	(no burden) 1---2---3---4---5---6---7 (unbearable)	**yes / no**
Communication problems	(never) 1---2---3---4---5---6---7 (continuously)	(no burden) 1---2---3---4---5---6---7 (unbearable)	**yes / no**
Pain	(never) 1---2---3---4---5---6---7 (continuously)	(no burden) 1---2---3---4---5---6---7 (unbearable)	**yes / no**
Sexual problems	(never) 1---2---3---4---5---6---7 (continuously)	(no burden) 1---2---3---4---5---6---7 (unbearable)	**yes / no**
Feelings of depression	(never) 1---2---3---4---5---6---7 (continuously)	(no burden) 1---2---3---4---5---6---7 (unbearable)	**yes / no**
Feelings of anxiety	(never) 1---2---3---4---5---6---7 (continuously)	(no burden) 1---2---3---4---5---6---7 (unbearable)	**yes / no**
Relationship issues	(never) 1---2---3---4---5---6---7 (continuously)	(no burden) 1---2---3---4---5---6---7 (unbearable)	**yes / no**
Worrying about the future	(never) 1---2---3---4---5---6---7 (continuously)	(no burden) 1---2---3---4---5---6---7 (unbearable)	**yes / no**
Problems with returning to work	(never) 1---2---3---4---5---6---7 (continuously)	(no burden) 1---2---3---4---5---6---7 (unbearable)	**yes / no**

Do you want to explain anything about your answers?.....

Have you experienced any other symptoms or complaints, that have not been addressed in this questionnaire? Please explain: .....

Fig. 1. The symptom questionnaire. This questionnaire was used to assess symptoms in glioma patients during the stable phase of the disease.

Importantly, since many glioma patients wish to be involved in decision-making concerning their treatment and care, it is critical to involve patients in prioritizing which symptoms to treat [14]. Consequently, we need to improve our understanding of whether patients would consider engaging in symptom management interventions during the stable phase of the disease.

The symptoms that patients with glioma, cancer, and neurological disease experience are known to co-occur, and might also influence each other [15–17]. For example, someone living with cancer or stroke might experience fatigue, consequently leading to physical inactivity, which might reinforce anorexia and further loss of physical fitness, again leading to fatigue [18–20]. Likewise, in glioma patients, fatigue and drowsiness, and also anxiety and depression are known to co-occur [2,16]. Symptom networks can provide insight into the complex nature of these co-occurring symptoms. These networks are defined as a collection of interconnected symptoms and have been used to analyze symptoms and HRQoL in patients with other types of cancer [17,21–23]. A network study on symptoms in cancer patients demonstrated that symptoms like sleeping problems, lack of energy, drowsiness, difficulty concentrating, and feeling irritable all co-occur and cluster together within a network of symptoms [23]. An exploratory network study in newly-diagnosed glioma patients showed that fatigue and motor dysfunction play a central role in a network of symptoms [16]. Central symptoms and symptom clusters in these networks may be particularly relevant targets for treatment, and understanding how symptoms interrelate might lead to a better understanding and thus treatment of patients' symptoms [21].

In this study, we aimed to identify the most frequent and burdensome symptoms in glioma patients during the stable phase and determine whether patients would consider treatment for these specific symptoms. As an exploratory analysis, we examined how symptoms are interrelated and visualized this as a symptom network. Gaining more insight into the symptoms that patients with stable disease experience and seek treatment for, could guide future symptom management strategies in glioma patients.

2. Materials and methods

2.1. Procedures and patients

We performed a retrospective study in patients with diffuse glioma visiting the Brain Tumor Center Amsterdam – a tertiary referral center for patients with brain tumors. The review board of the Amsterdam UMC location Vrije Universiteit Amsterdam reviewed and approved the protocol of an overarching study to collect clinical data in brain tumor patients (VUMC2012.362). Patients signed informed consent for the use of their clinical data for research purposes. The study was conducted in accordance with the World Medical Association Declaration of Helsinki [24].

As part of routine clinical care, patients completed a symptom questionnaire (Fig. 1) prior to the appointment with their treating physician. The questionnaire was used to determine the needs of the patient and develop a treatment strategy and symptom management plan (e.g. referral to a medical psychologist, rehabilitation program, or physical therapist).

We retrospectively identified adult patients with histologically confirmed diffuse glioma (WHO grade II-IV) with stable disease [25]. Stable disease was defined as 1) no radiological or clinical progression during and three months before completion of the questionnaire, 2) no current anti-tumor therapy during and three months before completion of the questionnaire and, 3) no corticosteroid use. Patients were excluded if they did not understand the Dutch language. Only one questionnaire per patient was included.

2.2. The symptom questionnaire

The Dutch symptom questionnaire was developed by clinicians at the Brain Tumor Center Amsterdam and aimed to assess the needs of glioma patients with stable disease. The questionnaire addresses seventeen items and was constructed based on the M.D. Anderson Symptom Inventory – Brain Tumor Module, the European Organization for Research and Treatment of Cancer brain cancer module, and our clinical experience with symptoms experienced by glioma patients [10,26,27]. Symptoms specifically linked to chemotherapy were not included in the questionnaire as patients were not on active treatment. The item "sexual problems" was also added because this topic is not often covered, even though sexual dysfunction is an important symptom in this population [28–30]. For each of the seventeen symptoms, patients rated how often they experienced the symptom in the past two weeks (frequency dimension) on a seven-point Likert scale and rated its burden (burden dimension) on a seven-point Likert scale, as well as stating whether they would consider treatment for that particular symptom with a yes/no question (treatment dimension). A higher score represents a higher frequency or burden. Additionally, the patient could elaborate on any additional symptoms with two open questions. Because of its intended use in clinical practice, the questionnaire itself was not validated. An English translation of this Dutch questionnaire is provided in Fig. 1.

2.3. Statistical analysis

Analyses were conducted using R (version 4.0.2) [31]. Values were presented as mean with standard deviation for normally distributed data and median with interquartile range (IQR) for skewed data. The top symptoms were defined as the five symptoms with the highest median score and percentage on all three dimensions (frequency, burden, treatment). For the calculation of the median scores, missing values were omitted. A score of 5, 6, or 7 out of 7 was classified as 'high'. Flow diagrams were used to visualize whether patients would consider treatment for each of the top five symptoms depending on the frequency and burden of their symptoms.

Correlations between the symptom frequency and burden dimensions, between the frequency and treatment dimensions, and between the burden and treatment dimensions were analyzed with Kendall's Tau correlation coefficients for each symptom. We determined the median and range of all these symptom-specific correlations for each dimension. A median Tau of $\leq$0.26 was

considered a weak correlation, 0.27 to 0.50 moderate and ≥0.51 strong [32]. We performed a bootstrapping analysis to determine the distribution and variance of scores of the symptoms in this population [33]. The median and interquartile range of the frequency and burden dimensions of the seventeen symptoms were bootstrapped using 10,000 samples by random selection with replacement with the 'Boot' package in R [31,34].

As an exploratory analysis, we visualized the frequency dimension of the symptom questionnaire as a symptom network based on a Spearman's partial correlation matrix using symptom network analysis [35]. The network consist of the seventeen symptoms and the links between symptoms represent the partial correlation coefficient between two symptoms after controlling for the other symptoms on a group level. Only patients with complete data were included. The network was regularized with EBICglasso with the tuning parameter set at 0.2 and was constructed with a spring layout with the package 'Qgraph' [22,36]. We visually inspected the network to identify possible clusters of symptoms. It is important to emphasize the exploratory nature of this analysis. Because of this, we did not examine the stability and accuracy of the network and therefore the symptom network should merely be used as a tool to visualize co-occurring symptoms [37].

3. Results

3.1. Inclusion and sample characteristics

Between October 2019 and February 2020 62 patients completed the symptom questionnaire. Thereafter, no more questionnaires were handed out because of the COVID-19 pandemic. Ten questionnaires were excluded because patients did not have a diffuse glioma (n = 4), had clinical or radiological progression (n = 3), were on active treatment (n = 1), filled in the questionnaire twice within a short period (n = 1), or had not given consent for the use of data for research purposes (n = 1). The resulting sample of 52 patients had a

Table 1
Sociodemographic and clinical characteristics.

N = 52	
Age in years, mean (SD)	50.1 (13.9)
Length of stable phase in months, median [IQR] *	28 [11–53]
Sex	
Male	32 (61.5%)
Female	20 (38.5%)
KPS	
70-80	12 (23.0%)
90	25 (48.1%)
100	15 (28.8%)
Hemisphere	
Left	25 (48.1%)
Right	27 (51.9%)
Predominant lobe	
Frontal	26 (50.0%)
Temporal	13 (25.0%)
Parietal	13 (25.0%)
WHO grade	
II	16 (30.8%)
III	15 (28.8%)
IV	21 (40.4%)
Histology	
Oligodendroglioma	20 (38.5%)
Astrocytoma	11 (21.2%)
Glioblastoma	21 (40.4%)
Molecular subtype	
IDH-wildtype	12 (23.1%)
IDH-mutant, non-codeleted	7 (13.5%)
IDH-mutant, 1p/19q codeleted	17 (32.7%)
No molecular characterization performed	16 (30.8%)
Previously had radiotherapy	
No	8 (15.4%)
Yes	44 (84.6%)
Previously had chemotherapy	
No	12 (23.1%)
Yes	40 (76.9%)
Diagnosed with epilepsy	
No	9 (17.3%)
Yes	43 (82.7%)

Data are presented as number of patients with % in brackets unless otherwise specified.
* Number of months the patient has been classified as being stable since the previous treatment. Abbreviations: SD, standard deviation; IQR, interquartile range; IDH, isocitrate dehydrogenase.

mean age of 50 years, 40% had a WHO grade IV glioma (n = 21) and 77% had a KPS score of 90 or 100 (n = 40), see Table 1.

3.2. Frequency and burden of symptoms

The top five symptoms were fatigue, memory problems, reduced physical fitness, difficulty concentrating, and drowsiness (see Fig. 2A and B). For example, fatigue had a median score on the frequency dimension of 4.5 (IQR 2.5). The median values per symptom are shown in Table 2. See Supplementary Figs. 1 and 2 for the bar plots of patients with WHO grade II/II and WHO grade IV glioma.

The majority of the patients rated at least one symptom with a high score (i.e. 5, 6, or 7) on the frequency dimension (77%) or the burden dimension (63%). Furthermore, patients often experienced multiple symptoms simultaneously: 54% of the patients rated three different symptoms or more with a high frequency. Seven patients reported additional symptoms that were not addressed in the questionnaire: feeling fuzzy, sensitivity to external stimuli, deaf and sensitive ears, word-finding problems, feeling unstable, walking problems, and itchy feet/legs.

3.3. Considering treatment for symptoms

Thirty-three patients rated at least one symptom with a high score on the burden dimension, and of those less than half of the patients (n = 14) stated they would consider treatment (see Fig. 2C and Table 2). In total, 35% of the patients stated they would consider treatment for at least one symptom. Of note, this question was left blank in 25%. The flow diagrams in Fig. 3A–E demonstrate how the patients that did or did not consider treatment for the top five symptoms answered the questions on frequency and burden dimensions. Patients who rated the frequency or burden dimension with a score of 5, 6, or 7 would consider treatment more often, compared to patients rating symptoms with a score of one or two.

Symptom frequency and considering treatment correlated moderately (median Kendall's Tau of 0.35, with a range of correlations of 0.24–0.57), as did symptom burden and treatment consideration (median Kendall's Tau of 0.38, range 0.28–0.61). Not surprisingly, the frequency and burden dimensions were strongly correlated (median Kendall's Tau of 0.84, range of 0.73–0.95). See Supplementary Fig. 3.

3.4. Robustness of the sampled data

A bootstrap analysis was performed to examine whether the large interquartile ranges around the median values, would be smaller if a larger sample would have been included. Results are detailed in Supplementary Table 1. The median values for all the symptoms were similar in the actual sample and the bootstrapped samples. The bootstrapped interquartile ranges were indeed smaller, suggesting that if we would have included a larger sample the distribution of results would be centered even more around the median.

3.5. Exploratory analysis: visualization of symptoms as a network

Data from 46 patients were used to visualize seventeen symptoms as a symptom network (Fig. 4). This network illustrates that symptoms often co-occur and can be visualized and interpreted as a network.

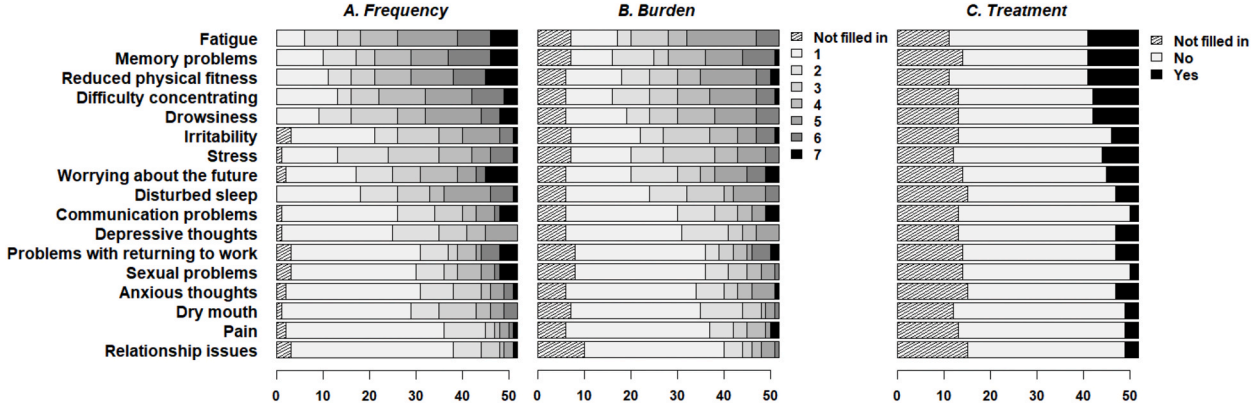

Fig. 2. Stacked bar plots of all scores per symptom. A. Stacked bar plots of the symptoms across the frequency dimension. B. Stacked bar plots of the symptoms across the burden dimension. C. Stacked bar plots of the symptoms across the treatment dimension. The x-axis represents the number of patients and the y-axis the seventeen symptoms. Fig. 2A and B shows the results of the frequency and burden dimensions on a seven-point Likert scale. A higher score depicts a higher frequency or burden. For example, in Fig. 2A the light grey box on the left side of the bar plot depicts the number of patients who answered '1, never' and the black box on the right side depicts the number of patients who answered '7, always' to the question 'How often in the past two weeks?'. Fig. 2C shows whether the patient would consider treatment. The plots also show the number of times the question was not filled in.

Table 2
Results of the symptom questionnaire.

Symptom	Frequency			Burden			Treatment
	Median	IQR	N	Median	IQR	N	Yes (%)*
Fatigue	4.5	[2.50]	52	4.0	[3.00]	45	21
Memory problems	4.0	[4.00]	52	4.0	[3.00]	45	21
Reduced physical fitness	4.0	[4.00]	52	3.0	[3.75]	46	21
Concentration problems	4.0	[3.25]	52	3.0	[3.00]	46	19
Drowsiness	3.5	[3.00]	52	3.0	[4.00]	46	19
Irritability	3.0	[3.00]	49	3.0	[3.00]	45	12
Stress	3.0	[2.00]	51	3.0	[3.00]	45	15
Worrying about the future	3.0	[3.75]	50	2.0	[4.00]	46	13
Disturbed sleep	2.5	[4.00]	52	2.0	[2.75]	46	10
Communication problems	2.0	[2.00]	51	1.0	[2.00]	46	4
Depressive thoughts	2.0	[2.00]	51	1.0	[1.00]	46	10
Problems with returning to work	1.0	[3.00]	49	1.0	[2.00]	44	10
Sexual problems	1.0	[3.00]	49	1.0	[1.25]	44	4
Anxious thoughts	1.0	[2.00]	50	1.0	[1.75]	46	10
Dry mouth	1.0	[2.00]	51	1.0	[1.00]	45	6
Pain	1.0	[1.00]	50	1.0	[1.00]	46	6
Relationship issues	1.0	[1.00]	49	1.0	[1.00]	42	6

Abbreviations: IQR, interquartile range; N, number.
* Percentage of patients that answered 'yes' to the question 'Would you consider treatment?'.

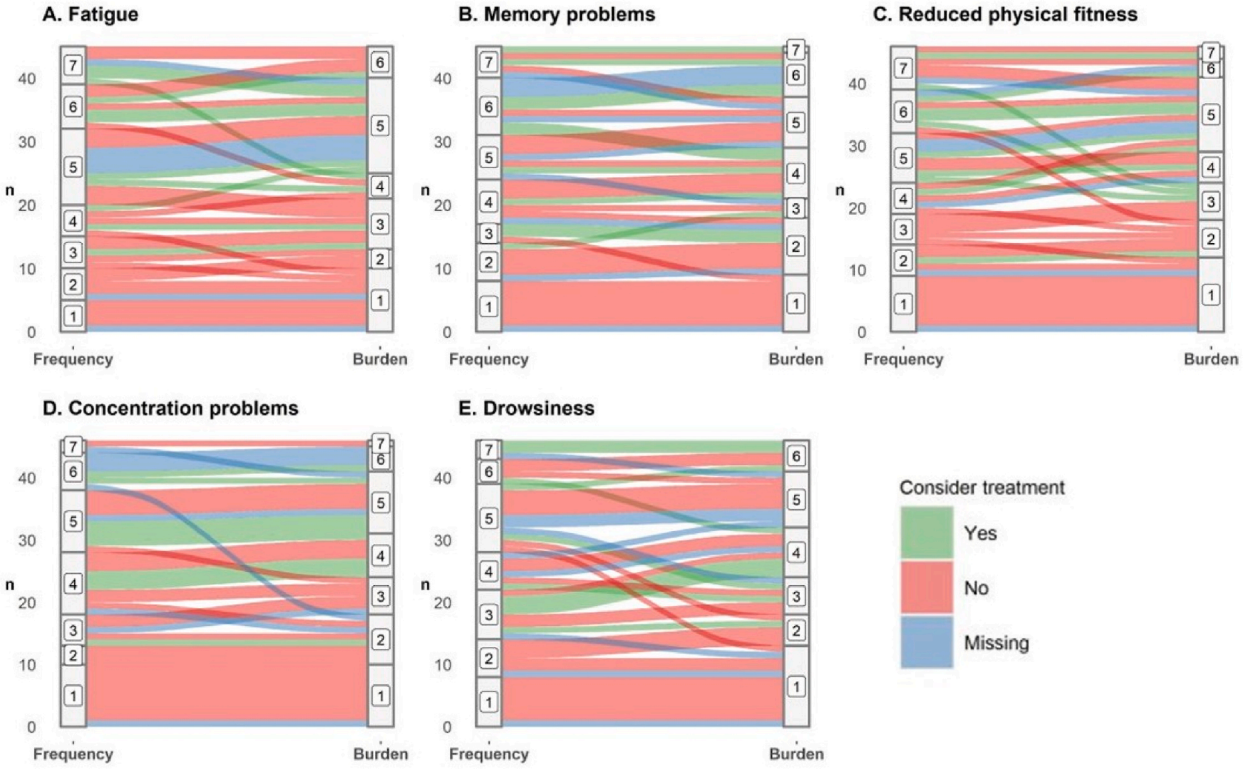

Fig. 3. Flow diagrams representing whether patients would consider treatment according to their frequency and burden scores. Figures A–E. Each figure presents a symptom. The left y-axis represents how patients scored the frequency of a symptom and the right y-axis how they scored the burden of that same symptom. The green lines from left to right represent patients who would consider treatment, red lines patients who do not consider treatment, and blue lines patients who left the treatment question blank. When a line is bigger, more patients filled in this specific combination of answers. For example, the large red line at the bottom of Fig. 3E represents the proportion of patients that scored both frequency and burden with a score of 1 and did not consider treatment. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4. Discussion

4.1. The most frequent and burdensome symptoms

The most frequent and burdensome symptoms in glioma patients with stable disease were fatigue, memory problems, reduced physical fitness, difficulty concentrating, and drowsiness. Not surprisingly, the symptoms that glioma patients reported in this study largely overlap with those reported in the literature [2,38,39]. Fatigue, drowsiness, and memory problems were also among the most prevalent symptoms in a study focusing on primary brain tumor patients during follow-up [10].

4.2. Management of symptoms

Whether a patient considered an intervention varied substantially between individuals and depended on which symptoms they experienced. Overall, whether patients would consider symptom management interventions correlated moderately with the frequency and burden of the experienced symptoms. Surprisingly the percentage of patients considering symptom management for at least one of the symptoms was relatively low: only one-fifth of the patients would consider treatment for fatigue, the most frequent and burdensome symptom. This finding, however, is not specific to glioma patients. Cancer patients often do not seek or want support for psychological symptoms [40–42]. Patient-reported barriers in seeking psychological support include a lack of information, not knowing services and treatment exist at all, a perceived overload with other medical appointments, no need for treatment, and practical issues, such as transportation [41–43]. In this study, patients often left the question on treatment blank. So, perhaps patients required more information in order to be able to answer this question. Additionally, perhaps patients would also prefer treatment for multiple co-occurring symptoms rather than for individual symptoms. To optimize symptom management, clinicians should aim at offering patients clear information on intervention options and the expected results [14].

Even though treating frequently experienced symptoms could improve HRQoL in glioma patients, only a small number of evidence-based interventions exist [39]. A systematic review of supportive-care interventions for adults with brain tumors identified ten randomized-controlled trials [44], of which only two interventions had a beneficial effect on HRQoL [45,46]. A home-based psychosocial intervention had a positive effect on multiple symptoms, like depression and stress, and HRQoL [45] and a study on acupuncture had a positive effect on HRQoL in astrocytoma patients with hemiparesis after surgery [46]. Other interventions aimed at improving the most frequent and burdensome symptoms identified in this study have been suggested: exercise might be beneficial for fatigue and physical functioning, and psychological interventions, such as cognitive rehabilitation therapy or acceptance and commitment therapy, could be beneficial in patients with fatigue, cognitive problems or anxiety and depression [47–53]. Cognitive

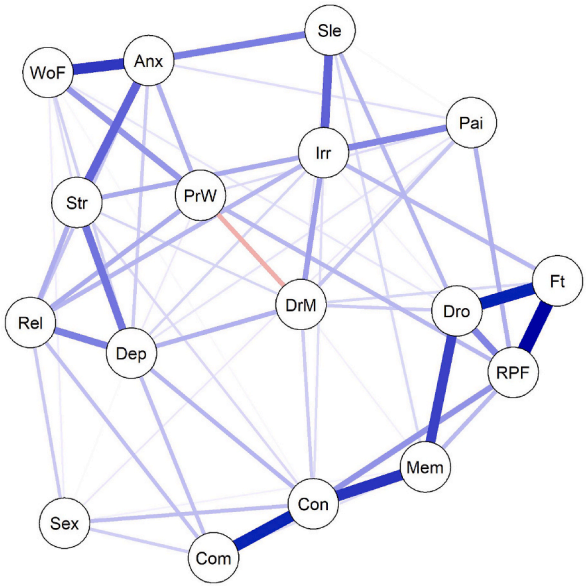

Fig. 4. A symptom network of the frequency of seventeen symptoms. Each circle represents the frequency dimension of one of the seventeen symptoms. An edge between two circles represents the partial correlation coefficient between two symptoms. A darker and wider line represents a larger partial correlation coefficient. A blue line represents a positive partial correlation and a red line represents a negative partial correlation. Because of the small sample size and relatively low tuning parameter, this network might include false-positive lines. The seventeen symptoms represented in the nodes above are **Anx** Anxious thoughts; **Com** Communication problems; **Con** Difficulty concentrating; **Dep**, Depressive thoughts; **DrM**, Dry mouth; **Dro**, Drowsiness; **Ft**, Fatigue; **Irr**, Irritability; **Mem**, Memory problems; **Pai**, Pain; **PrW**, Problems with returning to work; **Rel**, Relationship issues; **RPF**, Reduced physical fitness; **Sex**, Sexual **Sex**, Sexual problems; **Sle**, Disturbed sleep; **Str**, Stress; **WoF**, Worrying about the future.

behavioral therapy targeting fatigue has proven to be beneficial in patients with other types of cancer and might also be promising in glioma patients [54,55]. More experimental treatments, such as transcranial magnetic stimulation to improve cognitive deficits, are still under investigation [56,57].

4.3. Co-occurring symptoms

In this study, over half of the patients suffered from three or more co-occurring symptoms. As an exploratory analysis, we visualized symptoms as a network to explore how symptoms co-occur. Based on visual inspection of the network, some symptoms indeed seem to cluster and fatigue, reduced physical fitness, and drowsiness were strongly correlated. This was also the case for memory problems, concentration problems, and communication problems, and worrying about the future, stress, and anxious thoughts. Other studies investigating symptom networks and clusters of symptoms in cancer patients presented similar results. For example, a network study in cancer patients identified a "Psychological Symptom Cluster", with difficulty sleeping, worrying, feeling sad, feeling irritable, feeling nervous, difficulty concentrating, lack of energy, and feeling drowsy [23], and studies using different statistical methods found sleep-wake disturbance and fatigue to cluster together [58,59].

It must be noted that the presented network should be interpreted cautiously and should only be used as a visual illustration of the data. The number of observations in this current study was small and no stringent regularization techniques were used [35]. In future studies, our findings should be replicated by applying symptom network analysis to a larger sample. It could be worthwhile to study whether symptom management should focus on targeting the symptom network as a whole, instead of focusing on individual symptoms [60,61]. It has been hypothesized that highly connected symptoms in a network could be important treatment targets because they might also instigate changes in other symptoms [62]. This novel network approach can be a valuable addition to symptom management research.

4.4. Limitations

Due to the small sample size, we did not statistically test whether there are differences in experienced symptoms between tumor grades. However, symptoms do seem to be more frequent and burdensome in patients with lower-grade gliomas. Most studies report more symptoms and a poorer QoL in patients with a higher-grade glioma [63–66]. However, the study by Armstrong also reported some symptoms to be more prevalent in lower-grade gliomas [10]. Moreover, our findings could be influenced by selection bias since we only included patients in the stable phase of the disease, and patients with a lower-grade glioma were overrepresented in our sample [4]. Since patients with glioblastoma usually undergo extensive medical treatment and often suffer from progressive disease at a relatively early stage of the disease, the inclusion of a larger sample of glioblastoma patients might show different results. For future directives, including patients in other disease phases would also be of interest. The differences in symptom frequency and burden and the need for treatment across different tumor grades should be investigated in larger sample sizes.

We used a non-validated questionnaire that was developed for use in clinical practice. The questionnaire does largely overlap with questionnaires that are validated and the results of this study are mostly in line with the literature. Moreover, even though we did not do a power analysis and included a small sample of patients, bootstrapping suggested that the results were robust and generalizable to a larger population. Due to the COVID-19 pandemic, the distribution of the questionnaire came to a halt, because of healthcare resource prioritization, the inability of patients to visit the hospital, and to prevent bias because of COVID-related impact on symptoms and HRQoL.

5. Conclusion

In this observational study in glioma patients with stable disease, the most often reported symptoms were: fatigue, memory problems, reduced physical fitness, difficulty concentrating, and drowsiness. These symptoms should serve as a roadmap for future research on rational treatment strategies to alleviate interrelated symptoms. Despite the high prevalence of symptoms, the inclination to consider treatment was relatively low. Whether a patient would consider treatment varied substantially between individuals and different symptoms. Using symptom network analysis to understand how those symptoms co-occur could be a valuable addition to symptom research in glioma patients.

Author contribution statement

Jantine Geertruida Röttgering, Vera Belgers, Mathilde C.M. Kouwenhoven, Philip C. de Witt Hamer, Linda Douw and Martin Klein; Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Maaike Schuur, Tjeerd J. Postma, Claudia M. Nijboer and Myra E. van Linde: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no competing interests.

Abbreviations

HRQoL	Health-Related Quality of Life
IDH	Isocitrate dehydrogenase
IQR	Interquartile range
SD	Standard deviation

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e13278.

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