ZHAW School of Management and Law MSc in Business Administration Major Health Economics and Healthcare Management

Master Thesis

Effect of Inpatient Therapy on Quality of Life, General and Psychosocial Functioning, Psychological Impairment, and Symptoms Severity for Patients with Functional Neurological Disorders

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Management Summary

Functional neurological disorders (FND) are characterized by the presence of symptoms not caused by a classic neurological disorder. FND are among the most common causes of neurological disability and long-term outcome is poor. Treatment involves multidisciplinary care, including psychoeducation, psychological therapy, or physiotherapy. Since 2021, the Psychosomatic Medicine at Inselspital Bern offers the first specialized inpatient program for FND patients in Switzerland. This study evaluates the treatment effectiveness of this three weeks multidisciplinary inpatient therapy for FND patients, using patient-reported outcome measures (PROMs) and clinical data, providing a comprehensive assessment of therapy impact on quality of life (QOL), general and psychosocial functioning, psychological impairment, and symptom severity.

In a first step, a scoping review was conducted to identify studies on therapy programms for FND patients and to analyse the corresponding outcomes measures. In a second step, the data of patients, attending the three weeks multidisciplinary inpatient therapy at the Psychosomatic Medicine at Inselspital between July 2021 and April 2023, was analysed. The study included 43 adult patients with FND and collected data at three individual timepoints: at the beginning of therapy (entry), at the end of therapy (exit), and at a three months follow-up. The therapy consisted of physiotherapy, individual psychotherapy, medical consultations, and occupational therapy.

Significant improvement was found in clinical symptoms but no clear significant improvements in PROMs. QOL did not significantly improve across all patients, although there was a significant improvement in QOL at exit compared to entry for patients who were assessed at all three timepoints. General and psychosocial functioning did not show significant differences overall, but there was a significant reduction in impairment from entry to exit. Psychological impairment did not significantly change across all patients, but there was a significant decrease in mean depression scores from entry to exit and a significant increase again at follow-up compared to exit. Compared to the PROMs, the objectively assessed clinical data showed a significant improvement in symptoms at exit and follow-up over all patients.

The study found that clinical outcomes, as assessed by clinicians, did not align with PROMs. While clinical measures showed an improvement, patients did not report a corresponding increase in PROMs. This might suggest that patients have different expectations than clinicians, with patients focusing more on subjective feeling and coping with the disease. The findings indicate that PROMs were less sensitive to change over time compared to clinician-rated assessments. While previous literature on PROMs showed inconsistent results, literature on clinical outcome measures consistently demonstrated a reduction in symptoms. Thus, the findings of this study align with previous research, emphasizing the effectiveness of therapy in reducing symptoms of FND. However, this study must be replicated in a larger sample size, and incomplete data must be avoided to reduce a potential selection bias. Furthermore, FND subtypes and outpatient therapy must be considered. Overall, the study emphasizes the need to explore different outcome measures and the long-term effects of treatment for FND patients.

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Abbrevations

ANOVA	Analysis of variance
CBT	Cognitive behavioural therapy
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EQ VAS	EuroQoL visual analog scale
EQ-5D-3L	EuroQoL 5-dimension 3-level instrument
EQ-5D-5L	EuroQoL 5-dimension 5-level instrument
FND	Functional neurological disorder
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale - Subscale Anxiety
HADS-D	Hospital Anxiety and Depression Scale - Subscale Depression
ICD-10	International Statistical Classification of Diseases and Related Health
	Problems, 10 th Revision
PMDRS	Psychogenic movement disorder rating scale
PROMs	Patient reported outcome measures
QOL	Quality of life
SD	Standard deviation
S-FMDRS	Simplified Functional Movement Disorders Rating Scale
TAU	Treatment as usual
WSAS	Work and Social Adjustment Scale

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1. Introduction

1.1. Functional Neurological Disorders

Functional neurological disorders (FND), formerly known as conversion disorders, are defined by the presence of symptoms that are not caused by a classic neurological disorder (American Psychiatric Association, 2013). FND is a heterogeneous disease with multiple subtypes that manifests with variety of symptoms that can be different from patient to patient. The motor aspect of the disorder includes a wide array of symptoms (positive signs), such as functional weakness (global or one-sided), functional tremor, dystonia, difficulties in gait and balance, jerks or myoclonus (Hallett et al., 2022). Other aspects of the disorder include for example functional non-epileptic seizures, sensory manifestations, or speech impairments (Espay et al., 2018).

FND are among the most common causes of neurological disability and account for about 6% of neurology outpatient contacts (Carson & Lehn, 2016a). The incidence rate in the population is 4-12 per 100 000 per year, which is similar to Parkinson's disease and multiple sclerosis (Nielsen, Buszewicz, et al., 2017). Women are more commonly affected than men and the peak incidence is reached between the ages of 35 and 50 (Carson & Lehn, 2016b). The long-term outcome is poor. According to Gelauff et al., (2014) about seven years after treatment, approximately 40% of the patients have the same or more symptoms. The causes of FND are believed to be multifactorial and include exposure to psychological stressors and history childhood aversity. It often co-exists with psychological disorders, such as depression and anxiety, and other functional somatic disorders, which can further affect patients' QOL (Hallett et al., 2022).

Some studies suggest genetic factors that can predispose the development of the disorder (Apazoglou et al., 2018; Weber et al., 2023), however it is likely that a combination of diverse factors play a role in the origin of the disorder.

1.2. Current FND treatment

As the understanding of the disease has grown in the recent time, promising treatment options have emerged for patients suffering from FND. To increase effectiveness of treatment, the specific treatment options should follow general principles (Espay et al., 2018), putting emphasis on transparency of diagnosis and justification of chosen treatments, establishing treatment goals, and developing self-management strategies for symptoms. It is important to engage the patient in the process of diagnosis and treatment, establishing therapeutic two-way

communication (Hallett et al., 2022; Stone et al., 2016). Early diagnosis can help manage the symptoms and improves patient outcomes (Gelauff et al., 2014). Multidisciplinary care effectively targeting the individual symptoms is an important part of the treatment, often combining psychoeducation, psychological therapy, motor therapy and pharmacotherapy to target a varied range of symptoms.

1.2.1. Psychoeducation

Education plays an important role in facilitating the understanding and acceptance of a diagnosis (Lopez & LaFrance, 2022). By implementing strategies such as engaging, focusing, evoking, and planning, healthcare professionals can enhance treatment adherence, reduce seizure frequency, and improve the overall QOL (Tolchin et al., 2019). When providing psychoeducation, it is essential to address the factors that predispose, precipitate, and perpetuate the condition (LaFaver, 2020).

1.2.2. Psychological treatment of FND

In the past, psychological treatment of FND has been considered the method of choice. Forms of cognitive-behavioral therapy (CBT) and other psychotherapies, such as disorder-adapted CBT, multimodal cognitive behavioral–informed psychotherapy, CBT–oriented self-management, and interdisciplinary psychodynamic interpersonal therapy have shown promising results. The CBT has been recognized as gold standard in treatment of seizures, showing improvement in aspects like recognizing triggers and lowering the rates of psychogenic nonepileptic seizures (Goldstein et al., 2015; LaFrance et al., 2014).

1.2.3. Physical Treatment of FND

Physiotherapy and other forms of physical treatment, like occupational therapy and speech or language therapy, have gained increased attention in the past years as an effective treatment for motor symptoms related to FND, especially in cases of predominant motor manifestation of the disorder (Czarnecki et al., 2012; Nielsen et al., 2013). Occupational therapy can be helpful with a variety of symptoms associated with FND, especially regarding activities of daily living (Nicholson et al., 2020). However, no randomized trials on effect of occupational therapy alone were conducted.

Physiotherapy is used to treat functional movement disorders and limb weakness. The motor retraining during physiotherapy involves establishing the basic of simple movement patterns, with sequentially increasing complexity of the movement focusing on function, rather than specific impairments (Espay et al., 2018). Physiotherapy in FND is based on current understanding of the disorder and how individual components, such as misdirected attention

and abnormal sensorimotor perceptions, play a role in the motor manifestations of the disease (Edwards et al., 2013). As the manifested symptoms can vary among the FND patients, it is important for the physiotherapy to be tailored to the individual needs of each patient. The physiotherapy has been extensively tested in inpatient and outpatient settings, both frequently showing improvement in symptoms (Demartini et al., 2014; Nielsen, Buszewicz, et al., 2017). While the inpatient treatment might be of higher intensity, the outpatient treatment can offer advantage of a setting that resembles patients home environment more closely. For patients with functional symptoms, inpatient multidisciplinary approach seems to offer the greatest benefit (Gilmour & Jenkins, 2021). The frequency and intensity of physiotherapy, as well as the therapeutic setting offering the highest improvement are still open questions (Aybek & Perez, 2022), however aiming at patients' functional independence as the goal of therapy, rather than complete resolutions of symptoms, is an appropriate end-point (Gilmour & Jenkins, 2021).

1.2.4. Other Treatment Options

Some of the comorbid symptoms in FND, such as depression or anxiety, can be treated pharmacologically. Some other non-pharmacological interventions, like transcutaneous electrical stimulation, transcranial magnetic stimulation, and therapeutic sedation have been tried in small sample of patients, however the effectiveness remains controversial (Garcin et al., 2017).

1.2.5. Therapy at the Psychosomatic Medicine at Inselspital Bern

Since 2021, the Psychosomatic Medicine at Inselspital Bern offers a specialized three weeks intensive inpatient treatment program for FND patients. The inpatient therapy allows a higher treatment intensity and reduces environmental factors that may perpetuate symptoms.

Patients are referred to the Psychosomatic Medicine at Inselspital Bern from whole Switzerland, as so far there is no other FND specific center in the country. Patients with wide range of functional neurological symptoms, varied symptom duration and severity are treated in the inpatient clinic. Eligibility for treatment is determined in a preliminary consultation with the following criteria: a) disability primarily caused by FND, b) agreement to a multimodal treatment approach and c) exclusion of severe psychiatric or other comorbidities (Barbey et al., 2022).

Pretreatment, posttreatment, and follow-up assessments are performed at hospital admission (entry), at the discharge (exit) and three months after the discharge (follow-up).

To better serve this heterogeneous group of FND patients, it is important that the treatment options reflect the diversity of symptoms faced by each individual (Black, 2013; Hostettler et

al., 2018). In line with current recommendations, the therapeutic approach consists of a tailored multidisciplinary approach involving physiotherapists, psychotherapists, occupational therapists and neurologists (Espay et al., 2018; Hubschmid et al., 2015).

1.3. Measuring the effect of FND treatment

1.3.1. Patient Reported Outcome Measures

Patient reported outcome measures (PROMs) are standardized and validated questionnaires answered by patients to measure how they perceive their own health status and well-being (Dawson et al., 2010) and to provide information on effectiveness of a treatment (Marquis et al., 2006). PROMs measure patients' own perception on their health-related QOL, physical and psychosocial functioning, symptoms, and psychological well-being (Black, 2013; Hostettler et al., 2018; Marquis et al., 2006). Use of PROMs on these outcomes before and over the course of treatment can show changes on the individual patient level (Øvretveit et al., 2017).

Generic PROMs, e.g., the EuroQol five-dimensional descriptive system (EQ-5D) or the Work and Social Ability Scale (WSAS) measure overall QOL and general functioning. They can be used regardless of the disease and are comparable across different population and patient groups (Hostettler et al., 2018). Generic PROM instruments can be used for generalizing or comparing groups of patients across different conditions (Churruca et al., 2021). Disease-specific PROM instruments, such as e.g., the Hospital Anxiety and Depression Scale (HADS), measure the severity of a specific disease or a particular aspect of a disease. It is recommended to use both types of PROMs concurrently (Churruca et al., 2021).

Since PROMs are subjective and reflect patients' views and experiences, they do not replace more objective measurements and should be used in addition to clinical data (Devlin & Appleby, 2010).

1.3.2. Clinical Outcome

Using clinical data in addition to PROMs can provide a more comprehensive evaluation of therapy effectiveness. Clinical data offer objective measurements and observations related to the patients' health status.

By integrating clinical data with PROMs, clinicians and researchers can gain more wellrounded perspective on therapy effectiveness, taking into account both subjective patient experiences and objective health outcomes (Snyder et al., 2012). This comprehensive approach can enhance treatment evaluation, and overall patient care.

1.4. Aim of the study

The Psychosomatic Medicine at Inselspital Bern has only been treating FND patients with a specific inpatient therapy programme for two years, as the programme has been built up based on other therapy programmes with additional disorder-specific adaptions. Thus, there is no proof of effectiveness for the success of inpatient therapy for FND patients yet.

The aim of this study is to evaluate the effect of the three weeks multidisciplinary inpatient therapy at the Department of Neurology, Psychosomatic Medicine Unit, University Hospital Inselspital Bern, Switzerland for FND patients on QOL, general and psychosocial functioning, psychological impairment, and symptoms severity from entry to exit and at three months follow-up after discharge.

In contrast, no other disorders that are treated in the same inpatient setting are examined, no additional outcome measures other than the four mentioned are considered, the outcomes are only analysed regarding the three time points (entry, exit, and follow-up) and no control group is examined.

2. Methods

2.1. Literature Review

PubMed, Cochrane Library and Medline via Ovid were included in the literature search. The search was performed on April 13th, 2023, and included the concepts and search terms listed in Table 1.

Table 1: Literature sear	rch strategy
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Concent 1	Subject headings (MeSH	OR	Textwords (Title/Abstract):
FND	terms).	011	"Conversion Disorders" OR "Conversion
IND	"Conversion		Hysteria" OR "Conversion Reaction" OR
	Disorder"[Mash]		"Functional Movement Disorder*" OP
			"Eurotional Novelle disol Disordor" OR
			Functional Neurological Disorder OR
			Conversion Neurosis" OR "Conversion
			Neuroses" OR Astasia-Abasia OR "Astasia
			Abasia
Concept 2	Subject headings (MeSH	OR	Textwords (All Fields):
Intervention	terms):		Psychotherap* OR
	"Psychotherapy"[MeSH		invervention OR treatment* OR trial OR
	Terms], "Physical Therapy		"randomi*ed" OR therapy
	Modalities"[MeSH Terms],		
	"Physical Therapy		
	Specialty"[MeSH Terms]		
	"Occupational		
	Therapy"[MeSH Terms]		
Concept 3.1	Subject headings (MeSH	OR	Textwords:
EQ-5D-5L	terms):		"Life Quality" (Title/Abstract) OR "Health-
	"Quality of Life"[MeSH		Related Quality Of Life"(Title/Abstract) OR
	Terms		"Health Related Quality Of
	1		Life"(Title/Abstract) OR
			"*OOL"(Title/Abstract) OR "EO-5D"(All
			Fields) OR "EuroQOL"(All Fields)
Concept 3.2	Subject headings (MeSH	OR	Textwords (All Fields):
WSAS	terms):		"work and social adjustment scale" OR
	n.a.		"WSAS"
Concept 3.3	Subject headings (MeSH	OR	Textwords:
HADS	terms):		"Hospital Anxiety and Depression Scale"(All
	n.a.		Fields) OR HADS (All Fields) OR
			"anxiety"(Title/Abstract) OR "depression"
			(Title/Abstract)
Concept 3.4	Subject headings (MeSH		Textwords (All Fields):
S-FMDRS	terms):		"*Functional Movement Disorders Rating
	n.a.		Scale" OR "S-FMDRS" OR "PMDRS"

The search strategy was a combination of *Concept 1* AND *Concept 2* AND either of the *Concepts 3.1, 3.2. 3.3.* or *3.4.* In addition, the reference lists of the relevant articles were inspected, and topic specific publications were included. After excluding duplicate publications, the titles and abstracts of the remaining publications were screened. Publications

were included in the scoping review if they met the following criteria: 1) adult patients (>18 years) with an FND diagnosis, 2) participation in a therapy or intervention (i.e., psychotherapy, physiotherapy, psychoeducation, occupational therapy), 3) EQ-5D, WSAS, HADS or S-FMDRS were assessed as outcome measure at least before and after treatment, and 4) an association between the outcomes and the treatment was reported.

2.2. Therapy at the Psychosomatic Medicine at Inselspital Bern

2.2.1. Study Design

This is a retrospective, observational study, assessing treatment outcomes using data collected at three timepoints: entry, exit and follow-up. All the patients that received the multidisciplinary three weeks inpatient therapy between July 2021 and April 2023 were invited for psychometric assessment for quality management purposes and completed self-reported questionnaires within the first two days after intake (entry) and shortly before discharge (exit). The assessments were administered by a psychology intern and the patients' answers were recorded digitally using PsychoEQ (Institut für Verhaltenstherapie Berlin, Berlin). The clinical data were collected during a medical consultation. During the inpatient therapy at entry and exit, a board-certified neurologist examined the patients' symptoms.

After discharge, patients returned home to their usual setting or to subsequent rehabilitation. Post-discharge treatment was individualized for each patient and the therapy was continued on an outpatient basis. Three months after discharge (follow-up), the questionnaires were sent to the patients by mail. Additionally, patients were invited for a medical consultation with a board-certified neurologist to examine clinical symptoms at follow-up.

2.2.2. Sample size and inclusion criteria

The sample consists of 43 inpatients with FND treated between July 2021 and April 2023 in the Psychosomatic Medicine at Inselspital Bern.

Patients were included if they (a) fulfilled the diagnostic criteria of a conversion disorder (F.44.4, F44.5, F44.6 and/or F44.7) according to International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (World Health Organization, 2010), (b) were at least 18 years old, (c) with sufficient German or French proficiency, and (d) gave general written informed consent for further use of their data.

This research has been approved by the ethics committee of the Canton of Bern, Switzerland (project ID 2018-00493 and ID 2021-02214) and is in accordance with the Declaration of Helsinki.

2.2.3. Therapy

As first part of the inpatient therapy, a full neurological exam was performed including a review of all past medical records and results of previous tests. The diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013) and relied on positive signs (Stone & Carson, 2015). The DSM-5 takes into account that FND has different subtypes (e.g. motor FND: F44.4, non-epileptic attacks or seizures: F44.5, sensory symptoms: F44.6 or mixed symptoms: F44.7, coding according to ICD-10) (Figure 1). According to their symptoms and biopsychosocial situation, an individualized therapy was developed for each patient.

Somatic	Symptom	and Related disorders (309)
DSM 5	ICD 10	
300.82	(F 45.1)	Somatic symptom disoder (311) Specify if: with predominant pain Specify if: persistent Specify current severity: mild, moderate, severe
300.7	(F 45.21)	Illness anxiety disoder (315)
		Specify wehther: care seeking type, care avoidant type
300.11	(F44)	Conversion Disorder (Functional Neurological Symptom Disorder) Diagnostic Criteria: A. One or more symptoms of altered voluntary motor or sensory function. B. Clinical findings provide evidence of incompatibility between the symptom and recognized neurological or medical conditions. C. The symptom or deficit is not better explained by another medical or mental disorder. D. The symptom or deficit causes clinically significant distress or impairement in social, occupational, or other important areas of functioning or warrants medical
		evaluation. Specify symptom type:
	(F 44.4)	With weakness or paralysis
	(F 44.4)	With abnormal movement (e.g., tremor, dystonic movement, myoclonus, gait disorder)
	(F 44.4)	With swallowing symptoms
	(F 44.4)	With speech symptom (e.g., dysphonia, slurred speech)
	(F 44.5)	With attacks or seizures
	(F 44.6)	With anesthesia or sensory loss
	(F 44.6)	with special sensory symptom (e.g., visual, offactory, or hearing disturbance) With mixed symptom
	([44./)	with mixed symptom

Figure 1: Diagnostic and Statistical Manual of Mental Disorders DSM-5/ICD 10 (Barbey et al., 2022)

Good communication and explanation of the diagnosis is the first step of the therapeutic approach (Barbey et al., 2022; Stone & Carson, 2011), especially because having a clear diagnosis is a great relief for many patients and prevents repeated and unnecessary medical examinations (Stone et al., 2016).

The multidisciplinary therapy approach at the Psychosomatic Medicine at Inselspital Bern is partly based on the Physio4FMD trial from England (Nielsen et al., 2019), where patients in the intervention group received a specialized three weeks therapy program, that included 45-60 minutes of physiotherapy twice a day while the control group received the «treatment as usual» (TAU) which was a referral to a community physiotherapy. However, the frequency and amount of physiotherapy sessions differed between centers. The trial aimed to evaluate the effectiveness of specialized physiotherapy compared to TAU in reducing disability. Furthermore, Nielsen et al. (2019) aimed to evaluate the effectiveness of the intervention compared to TAU in regards of health-related QOL, anxiety and depression, work status, and somatic symptoms. Due to COVID-19, the study has been delayed and the outcomes have not yet been published (Marston et al., 2023).

During the course of the inpatient therapy at the Psychosomatic Medicine at Inselspital Bern, the main focus laid on intensive physiotherapy, which usually took place twice a day for 45 minutes. All patients received also individual psychotherapy, medical consultations, and occupational therapy once or twice a week for 60 minutes each. Depending on the patient's condition, occupational therapy, psychotherapy, and physiotherapy were additionally provided in a group setting. Furthermore, psychoeducational knowledge was developed together with the patient and with the help of a therapy notebook. After discharge the patients continued with the therapy in an outpatient setting.

2.3. Outcome Measures

2.3.1. Quality of life

To assess the change in patients' QOL in response to three weeks of inpatient therapy, the EQ-5D-5L questionnaire was used (Appendix 1). The EQ-5D provides a comprehensive framework for assessing and assigning value to five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The three-level version of the EQ-5D (EQ-5D-3L) was introduced in 1990 (EuroQol Group, 1990). Each dimension is divided in three categories: no problems, some problems, and extreme problems (Brooks, 1996). To further improve the sensitivity, a five-level version was established that included five levels of severity for each dimension (Level 1: indicating no problem, Level 2: indicating slight problems, Level

3: indicating moderate problems, Level 4: indicating severe problems, Level 5: indicating extreme problems) (Van Hout et al., 2012). The questions in the survey can help to determine specific health state of the patient, where each distinct dimension of health is assigned a single digit in a 5-digit health-state code. For example, health code of 11145 might indicate no problems with general mobility, self-care and usual activities; however, it would also indicate severe pain and extreme depression/anxiety. With this coding system, a total of 3125 possible health states can be determined (Van Hout et al., 2012).

In addition, fine changes in patients' perceived health state can be assessed over time using the EQ visual analog scale (EQ VAS), where the patient indicates on their current health state on a scale of 0-100 (from the worst imaginable to best imaginable).

After the collection of the last questionnaire at the follow-up period, the results were evaluated and presented as 1) EQ-5D-5L index value, and 2) EQ VAS at each timepoint. The index value was derived by applying a formula that attaches values (weights) to each of the levels in each of the dimensions. As the evaluation method differs between countries, the EQ-5D-5L Index Value Calculator, Version 2.0 was used with the value set for Germany (EuroQol, 2023; Van Hout et al., 2012).

2.3.2. General and psychosocial functioning

To determine the change in patients' functioning in response to three weeks of inpatient therapy, the WSAS was used (Mundt et al., 2002) (Appendix 2). The WSAS is a simple self-reported scale measuring functional impairment attributable to a known condition. The five-item scale measures impairment in ability to work, home management, social leisure activities, private leisure activities and close relationships, on a scale of 0-8 (from not at all impaired to very severely impaired). The German language version of the questionnaire has been validated (Heissel et al., 2021) and showed good convergent validity, criterion validity, strong internal consistency, and good sensitivity of the instrument.

After completing the questionnaires, the scores were summed up for each patient. The scores were interpreted as follows: score above 20 suggested high degree of impairment and moderately severe or worse clinical symptoms. Scores between ten and 20 were associated with significant functional impairment but less severe clinical symptoms. Scores below ten were associated with individuals not showing any functional impairment (Mundt et al., 2002).

2.3.3. Psychological impairment

To evaluate psychological distress and change in depression and anxiety index, in response to three weeks of inpatient therapy, the HADS was applied (Appendix 3) (Zigmond & Snaith,

1983). The HADS focuses on non-physical symptoms associated with depression (HADS-D) and anxiety (HADS-A), which often co-exist, using seven questions related to depressive symptoms and seven questions related to anxiety. The questionnaire has been developed to identify depression and anxiety disorders among diverse patient populations in non-psychiatric hospital clinics. It has been extensively validated (Bjelland et al., 2002), also in German population (Hinz & Brähler, 2011; Petermann, 2011). The items are scored on a 4-point Likert scale, ranging from 0 to 3. The total score represents the sum of the 14 items (in a range between 0-42), and for each subscale (HADS-A and HADS-D) the score is the sum of the respective seven items. For both scales, the scores were assessed as follows: < 7: non-cases, 8–10: Mild, 11–14: Moderate, 15–21: Severe (Petermann, 2011).

2.3.4. Clinical symptoms

To assess the evolution of objective clinical symptoms, in this case abnormal movements of psychogenic nature, in response to three weeks of inpatient therapy, a simplified version of Functional Movement Disorders Rating Scale (S-FMDRS) (Appendix 4) was used (Nielsen, Ricciardi, et al., 2017). The S-FMDRS is based on the Psychogenic Movement Disorders Rating Scale (PMDRS) (Hinson et al., 2005). The original PMDRS scale rated ten phenomena (rest tremor, action tremor, dystonia, chorea, bradykinesia, myoclonus, tics, athetosis, ballism, cerebellar incoordination), two functions (gait, speech), and 14 body regions in a comprehensive manner. The scale has been extensively validated and showed good sensitivity and inter-rated reliability. However, the association of scored symptom to specific neurological disease limits the usefulness and application in the clinical setting of FND. Moreover, the scale excludes functional weakness, which is one of the most common functional neurological symptoms. Thus, Nielsen et al., (2017) developed a simplified scale specific for scoring movement disorders resulting from FND. Several modifications were made to the original scale: 1) the number of body regions have been reduced from 14 to seven (face & tongue, head & neck, left upper limb & shoulder girdle, right upper limb & shoulder girdle, trunk & abdomen, left lower limb, and right lower limb). 2) The nature of the movement disorder (e.g. tremor, akinesia) has been removed and raters only need to indicate presence or absence of abnormal movement. 3) The severity score has been reduced to rating from 0 to 3 (0=none, 1=mild, 2=moderate, 3=severe), as opposed to 0-4. 4) The rating of duration of symptom has been decreased to score from 0 to 3 (0=none; 1=symptomatic movement spotted at least once or only a few times; 2=symptom is intermittent but frequent, so that there are periods during which it is absent or does not affect purposeful movement; 3=the symptom is evident continuously). The S-FMDRS also rates speech and gait. The scale has been validated against PMDRS, with good

inter-rating reliability for three neurologists, as well as good validity against other standardized tests. The scale has been used for evaluation of symptoms in FND patients in other studies (Schmidt et al., 2021; Věchetová et al., 2018).

In the current study, the examination and rating of symptoms was performed by a boardcertified neurologist. The total score represents the sum of severity and duration per body regions with a maximum score of 36.

2.4. Statistical Analysis

Through statistical analysis of the collected data, it was aimed to determine if the three weeks multidisciplinary inpatient therapy had a significant effect on QOL, general and psychosocial functioning, psychological impairment, and symptoms severity of FND patients. The effect of the therapy might be reflected in a significant difference between timepoints (entry, exit, follow-up).

The statistical analyses were performed using R statistical software Version 2023.03.1. The mean summary score (WSAS, HADS, S-FMDRS), or the mean index value and mean VAS score (EQ-5D-5L), respectively, were calculated over all patients, using all the available patient data for the corresponding timepoints. The significance level was set at alpha=0.05. Data was examined for normal distribution of the data using Shapiro-Wilk test of normality. Further, data were inspected for outliers and for homogeneity of variance using Levene's test for equality of variance. In a first step, repeated measures analysis of variance (ANOVA) with the factor *timepoint* was computed to assess the change in impairment over all patients across timepoints (entry, exit, follow-up) in response to the treatment. To determine which pairwise comparisons of means (i.e., entry-exit, exit-follow-up, entry-follow-up) contribute to the overall found significant difference between time points, a post-hoc model was created, and a multiple comparison correction (Bonferroni) applied.

In a second step, in the framework of post-hoc multiple comparison, the analyses excluding missing data and run analyses for patients with data for all three timepoints (entry, exit, and follow-up) was repeated. Differences between the timepoints (entry vs. exit, entry vs. follow-up, and exit vs. follow-up) were investigated. Wilcoxon rank sum tests were used on non-parametric data, while t-tests were applied on parametric data. Outcomes were adjusted for multiple comparison correction (Bonferroni).

3. Results

3.1. Literature

The literature search identified 156 publications across the three databases. 6 publications were additionally identified through other sources leading to a total of 162 publications. 23 were excluded due to duplication. An initial screening of the title and abstract resulted in the exclusion of further 75 publications. 64 studies passed screening for eligibility, at which 50 studies were excluded. A total of 14 publications was included in the scoping review according to the criteria 1) - 4) (see 2.1. Literature review). The flow chart of the literature search process is shown in Figure 2.



Figure 2: Flow chart of literature search process

An overview of the diagnosis, study design, sample size, interventions, timepoints, and main findings for the respective outcome measures of the included studies are listed in Tables 2-5.

Table 2: Overview o	of studies with outc	come EQ-5D			
Authors	Diagnosis	study design / sample size	Interventions / Arms	Timepoints	EQ-5D-5L
Nielsen et al. 2015	Motor	Observational treatment study: n=45	5-day specialist physiotherapy programme	baseline end treatment 3 month follow-up	EQ-5D-5L: • Mean index scores: baseline=0.35 (±0.43), 3m=0.47 (±0.8) Gain=0.125 (±0.065). • Significant increase in index scores from baseline and 3m follow-up
Nielsen et al. 2017	Motor	RCT: Intervention n=60 TAU n=57	 Intervention = Inpatient physiotherapy TAU 	Baseline 4 week follow-up 6 month follow-up	EQ-5D-5L: • Mean index in treatment= $0.34 (\pm 0.3)$, and in control = $0.26 (\pm 0.04)$ • Mean improvement= $0.08 (0.05)$
Petrochilos et al. 2020	Mixed symptoms	Observational treatment study: n=78	5-week outpatient programme	entry exit 6-month follow-up	EQ-VAS (SD) scores: entry=50 (±25), exit=60 (±25), 6m follow-up= 59 (25) p<0.001
Table 3: Overview c	of studies with outc	come WSAS			
Authors	Diagnosis	study design / sample	Interventions / Arms	Timepoints	WSAS
Chen et al. 2014	Seizures	RCT: 1) Interv. n=30 2) TAU n=34	 group psychoeducational sessions routine seizure clinic follow-up visits 	baseline 3 month (follow-up 1) 6 month (follow-up 2)	 Mean (SD) scores before treatment: intervention=23.05 (1.54), TAU=24.17 (±1.69) Mean (SD) scores at 3m follow-up: intervention=18.4 (±1.91), TAU=25.52 (±1.95), p=0.013 At 6m follow-up: intervention=18.75 (±1.85); TAU=24.86 (±2.15), p=0.038
Cope et al. 2017	Seizures	Observational treatment study: n=19	CBT-based group psychoeducation	pre treatment post treatment	Mean (SD) scores: from pre=16.35 (\pm 11.4) to post-treatment=13.00 (\pm 10.38) p=0.105

Authors	Diagnosis	study design / sample	Interventions / Arms	Timepoints	WSAS
Nielsen et al. 2015	Motor	Observational treatment study: n=45	5-day specialist physiotherapy programme	baseline end treatment 3 month follow-up	• WSAS scores improved significantly over time from start 24.2 (\pm 8.0) to end=23.0 (\pm 7.6) (p=0.015), and 3m and follow-up 21.0 (\pm 7.2) (p<0.001)
Nielsen et al. 2017	Motor	RCT: 1) Interv. n=60 2) TAU n=57	 Inpatient physiotherapy TAU 	Baseline 4 week follow- up 6 month follow-up	 No significant differences between arms follow-up (corrected for differences in baseline) Mean WSAS (SD) scores: interv.=20.2 (±10.5), TAU=26.9 (±10.2)
Petrochilos et al. 2020	Mixed symptoms	Observational treatment study: n=78	5-week outpatient programme	entry exit 6-month fu	 Significant increase inMean (SD) score from entry=20.5 (±17) to exit=15 (±13) and 6m follow-up=14 (13) p<0.001
Wiseman et al. 2016	Seizures	Observational treatment study: n=25	Brief manualised psychoeducation	pre treatment post treatment	 No significance in WSAS scores post compared to pre Median (SD): pre =26 (±17.9), post=20.5 (±14) p=0.122
Table 4: Overview	of studies with outco	ome HADS			
Authors	Diagnosis	study design / sample	Interventions / Arms	Timepoints	HADS
Conwill et al. 2014	Mixed symptoms	Observational treatment study: n=16	CBT-based group psychoeducation	pre treatment post treatment	 No significant improved HADS-A and HADS-D mean scores from start to end treatment (p>0.05) HADS-A: pre=8.6 (±6), post=7.8 (±5), p=0.34 HADS-D: pre=9.1 (±5.2), post=8.4 (±5), p=0.46

Authors	Diagnosis	study design / sample	Interventions / Arms	Timepoints	HADS
Demartini et al. 2014	Mixed symptoms	Observational treatment study: n=66	Specialist inpatient multidisciplinary rehabilitation	pre treatment post treatment 1 year follow- up	 Significant decreas in HADS scores compared after to before treatment Mean (SD) HADS scores: pre=15.8 (±8.5), post=13.3 (±8.2), p<0.005
Goldstein et al. 2004	Motor	Observational treatment study: n=16	CBT	pre treatment post treatment 6 month follow-up	 Significant improvements in HADS A and HADS-D mean scores from pre- to post-treatment (p<.05), effect sustained at 6m follow-up HADS-A: pre =10.1 (±5.6), post=7.8 (±5.5), and 6m=8.1 (±6.7) HADS-D pre-treatment=6.8 (±3.6), post=4.6 (±4.2), and 6m=4.6 (±5.1)
Goldstein et al. 2010	Seizures	RCT: Intervention n=66 TAU n=59	1) Intervention = CBT & TAU 2) TAU	Baseline End treatment (4m) 6 month follow-up	No significance for group or time found • Mean (SD) HADS-A Baseline: Interv.=8.8 (±4.9), TAU=9.0 (±4.8). End: Interv.=7.9 (±3.6), TAU=88.8 (±4.8). Follow-up: Interv.=7.2 (±5.2), TAU=8.8 (±5.2) • Mean (SD) HADS-D: Baseline: Interv.=6.7 (±4.0), TAU=7.9 (±5.1), End: Interv.=6.2 (±4.1), TAU=7.0 (±4.9), Follow-up: Interv.=5.7 (±5.3), TAU=7.4 (±5.2)
Nielsen et al. 2015	Motor	Observational treatment study: n=45	5-day specialist physiotherapy programme	baseline end treatment 3 month follow-up	 No significant improvement in HADS-A mean (SD): Baseline=7.1 (±4.4), end=6.1 (±4.7), follow-up=6.9 (±4.6) (p=.114) No significant improvement in HADS-D mean (SD) scores. Baseline=6.0 (±3.9), end of treatment=5.3 (±4.0), 3m follow- up=6.0 (±4.6) (p=0.96)
Nielsen et al. 2017	Motor	RCT: Intervention n=60 TAU n=57	 Intervention = Inpatient physiotherapy TAU 	Baseline 4 week follow-up 6 month follow-up	 No significant changes between intervention and TAU at 6m follow-up for HADS-A and HADS-D HADS-A (SD) at 6m follow-up: Intervention arm=6.9 (±4.8), TAU=7.9 (±5.6) HADS-D (SD) at 6m follow-up: Intervention arm=5.2 (±3.9), TAU=8.4 (±5.0)

Faul etMotorObservationalone-weekpre treatmentsignificant reduction in post-treatment PMDRal. 2020treatmentmultidisciplinarypost treatmentsignificant reduction from pre to post: 17.1(5.3), prestudy:al. 2020treatmentmean reduction from pre to post: 17.1(5.3), prestudy:impatientSchmidtMixedObservationalmultidisciplinarypost treatmentSchmidtMixedObservationalmultimodalpre treatmentstudy:treatmentinpatientpost treatmentfollow-up:study:treatmentinpatientpost treatmentfollow-up:study:treatmentfollow-uppre-11, post=4, follow-up=3, p<0.001study:n=3112 weeks CBTpre treatmentsignificant reduction in PMDRS scores.Jacob etMotorClinical trial12 weeks CBTpre treatmentsignificant reduction in PMDRS scores.Jacob etMotorObservationalone-weekpre treatmentsignificant reduction in PMDRS scores.Jacob etMotorObservationalone-weekpre treatmentpre: 34.3(17.1), post: 7.4(10.8), p<0.001Jacob etMotorObservationalone-weekpre treatmentsignificant reduction in PMDRS scores.Jacob etMotorObservationalone-weekpre treatmentsignificant reduction in PMDRS scores.Jacob etMotorObservationalone-weekpre treatmentsignificant reduction in PMDRS scores.Jacob etMotorObservational </th <th>Authors</th> <th>Diagnosis</th> <th>study design / sample</th> <th>Interventions / Arms</th> <th>Timepoints</th> <th>S-FMDRS / PMDRS</th>	Authors	Diagnosis	study design / sample	Interventions / Arms	Timepoints	S-FMDRS / PMDRS
SchmidtMixedObservationalmultimodalpre treatmentsignificant reduction of S-FMDRS scores afteet al.symptomstreatmentinpatientpost treatmentfollow-up:2021study:treatmentfollow-up:follow-up:2021n=31follow-upfollow-up2021n=31follow-upfollow-up2021n=31follow-upfollow-up2021n=15follow-upsignificant reduction in PMDRS scores.al. 2019n=15post treatmentsignificant reduction in PMDRS scores.Jacob etMotorObservationalone-weekpre treatmentJacob etMotorObservationalone-weekpre treatmentstudy:inpatientsignificant reduction in PMDRS scores.al. 2018treatmentmultidisciplinarypost treatmentstudy:inpatientsignificant reduction in PMDRS scores.	Faul et al. 2020	Motor	Observational treatment study: n=14	one-week multidisciplinary inpatient treatment	pre treatment post treatment	significant reduction in post-treatment PMDRS scores mean reduction from pre to post: $17.1(5.3)$, p<0.0001
Espay etMotorClinical trial12 weeks CBTpre treatmentsignificant reduction in PMDRS scores.al. 2019n=15post treatmentpre: 34.3(17.1), post: 7.4(10.8), p<0.001Jacob etMotorObservationalone-weekpre treatmentJacob etMotorObservationalone-weekpre treatmentsignificant reduction in PMDRS scores.al. 2018treatmentmultidisciplinarypost treatmentstudy:inpatientpost treatmentpre: 30(11.8), post: 12.3(9.9), p<0.01	Schmidt et al. 2021	Mixed symptoms	Observational treatment study: n=31	multimodal inpatient treatment	pre treatment post treatment 5 month follow-up	significant reduction of S-FMDRS scores after the rapy and sustained at follow-up: pre=11, post=4, follow-up=3, p<0.001
Jacob etMotorObservationalone-weekpre treatmentsignificant reduction in PMDRS scores.al. 2018treatmentmultidisciplinarypost treatmentpre: 30(11.8), post: 12.3(9.9), p<0.01study:inpatientinpatientpre: 30(11.8), post: 12.3(9.9), p<0.01	Espay et al. 2019	Motor	Clinical trial n=15	12 weeks CBT	pre treatment post treatment	significant reduction in PMDRS scores. pre: $34.3(17.1)$, post: $7.4(10.8)$, $p<0.001$
n=32 treatment	Jacob et al. 2018	Motor	Observational treatment study: n=32	one-week multidisciplinary inpatient treatment	pre treatment post treatment	significant reduction in PMDRS scores. pre: 30(11.8), post: 12.3(9.9), p<0.01

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3.2. Multidisciplinary inpatient therapy for FND

Between July 2021 and April 2023, 43 FND patients attended the three weeks inpatient therapy at the Psychosomatic Medicine at Inselspital Bern. Analysis was performed on all 43 patients who completed the three weeks therapy. However, some of the data were not available for all the patients at all three timepoints. An overview of the collected data is given in Figure 3. The reasons for dropouts and missing data were not individually recorded but were mainly due to patient's lack of language skills, too poor physical condition for the interview.



Figure 3: Overview of patients and collected outcome measures

3.2.1. Demographic and clinical characteristics

The baseline characteristics of the patients collected at entry are illustrated in Table 6 and Figure 4. The sample consisted of 14 males, 28 females and one non-binary person, with a mean age of $35.5 (\pm 15.4)$. Most patients (n=31) received the diagnosis 1-5 years ago. About half of the patients (n=20) have also been in treatment for 1-5 years. While two patients have had a diagnosis 1-3 months ago, six patients have been in treatment for this time.





Figure 4: Symptoms onset and duration of treatment

3.2.2. Quality of life

At entry, n=35 patients were completed the questionnaire, at exit, n=24 patients completed the questionnaire, and at three months follow-up, n=20 participated in the evaluation. Eleven patients that were assessed at the entry timepoint did not participate in the exit questionnaire and 15 patients evaluated at entry were not available for the follow-up. As two out of three timepoints showed normal distribution and ANOVA can – to some extent - tolerate data that is non-normally distributed with only a small effect on the Type I error, the assumption of normal distribution were regarded to be fulfilled.

The mean EQ-5D-5L index value (standard deviation (SD)) was 0.62 (\pm 0.24) at entry, 0.69 (\pm 0.21) at exit, and 0.68 (\pm 0.17) at the follow-up, which showed no significant difference in the timepoints (*F*(2,76)=0.953, *P*=0.39, Figure 6).

The mean EQ VAS (SD) was 37.4 (\pm 21.1) at entry, 48.5 (\pm 21.2) at exit, and 47.0 (\pm 22.2) at follow-up, with no significant difference in timepoints (*F*(2,65)=1.252, *P*=0.23, Figure 5).



Figure 5: Repeated ANOVA (factor timepoint) for EQ-5D-5L index value and EQ VAS Boxplot showing the mean (horizontal line) and the box representing the 25th or 75th interquartile range, respective. The error bars represent the max or mind value, respectively. The red dot indicates the group mean.

A total of 13 patients completed the entire study assessment at all three timepoints. To evaluate the distribution of data, Shapiro-Wilk test of normality was performed. The EQ-5D-5L index value was normally distributed for entry, and follow-up. However, for exit, data was slightly skewed (entry p=0.24, exit p=0.013, follow-up p=0.48). The EQ VAS values for entry, and exit were normally distributed, while the follow-up values were slightly skewed (entry p=0.20, exit p=0.31, follow-up p=0.014).

To account for the distribution, the data was analyzed using t-tests on parametric data and Wilcoxon rank test on non-parametric data. The patients did not show a significant difference in their EQ-5D-5L index values between timepoints (Figure 6), but a trend towards a higher EQ VAS score at exit compared to entry (Figure 7). Analyses were adjusted for multiple comparison correction (Bonferroni).



Figure 6: t-tests and Wilcoxon rank tests for EQ-5D-5L index score

Boxplot showing the mean (horizontal line) and the box representing the 25th or 75th interquartile range, respective. The error bars represent the max or mind value, respectively. The red dot indicates the group mean. Abbreviations: ns = not significant, SD = standard deviation



Figure 7: t-tests and Wilcoxon rank tests for EQ VAS

Boxplot showing the mean (horizontal line) and the box representing the 25th or 75th interquartile range, respective. The error bars represent the max or mind value, respectively. The red dot indicates the group mean. Abbreviations: ns = not significant, VAS = visual analog scale, SD = standard deviation

3.2.3. General and psychosocial functioning

The WSAS questionnaire completed n=36 patients at entry, n=21 at exit, and n=20 at three months follow-up. 15 patients that participated at the entry timepoint did not take part in the exit assessment, whereas 16 patients evaluated at entry did not participate in the follow-up.

Data was normally distributed across the three measurement timepoints. At the entry, the mean (SD) disability level of patients measured by WSAS was 26.1 (\pm 7.8), indicating a high degree of impairment and severe clinical symptoms. The mean disability level dropped slightly to 25.2 (\pm 8.1) at exit and further reduced at three months follow-up to 23.2 (\pm 8.2). There was no significant effect between the timepoints (*F*(2,72)=2.045, *P*=0.137, Figure 8).



Figure 8: Repeated ANOVA (factor timepoint) for WSAS Boxplot showing the mean (horizontal line) and the box representing the 25th or 75th interquartile range, respective. The error bars represent the max or mind value, respectively. The red dot indicates the group mean. Abbreviations: ns = notsignificant, SD = standard deviation

Ten patients completed the entire study assessment at all three timepoints. Shapiro-Wilk test was performed to assess the normality of WSAS summary score distribution. The data showed normal distribution for entry, exit, and follow-up (entry p=0.94, exit p=0.52, follow-up p=0.15). The data was analyzed using t-tests and adjusted for multiple comparison correction (Bonferroni). The patients showed significant difference in their WSAS scores from entry to exit (p=0.0103). However, there was no significant difference in WSAS score between entry and follow-up, or between exit and follow-up (Figure 9).



Figure 9: t-tests for WSAS summary scores

Boxplot showing the mean (horizontal line) and the box representing the 25th or 75th interquartile range, respective. The error bars represent the max or mind value, respectively. The red dot indicates the group mean. Abbreviations: ns = not significant, SD = standard deviation

3.2.4. Psychological impairment

For the HADS questionnaire, n=42 patients were registred at entry, n=36 at exit, and n=19 patients at three months follow-up. Six patients who were assessed at the entry timepoint did not participate in the exit assessment, while 23 patients who were evaluated at entry did not complete the follow-up assessment.

For HADS anxiety, the mean summary scores (SD) were 7.2 (\pm 4.6) at entry, 5.6 (\pm 4.1) at exit, and 5.6 (\pm 3.3) at the follow-up showing no significant difference in timepoints (*F*(2,94)=1.753, *P*=0.179, Figure 11).

Data for HADS depression scores were normally distributed. The mean summary scores (SD) were 6.3 (\pm 4.0) at entry, 4.8 (\pm 3.5) at exit, and 6.0 (\pm 2.9) at the follow-up, again, showing no significant difference in timepoints (*F*(2,94)=1.726, *P*=0.184, Figure 10).



Figure 10: Repeated ANOVA (factor timepoint) for HADS Anxiety summary scores and HADS Depression summary scores Boxplot showing the mean (horizontal line) and the box representing the 25th or 75th interquartile range, respective. The error bars represent the max or mind value, respectively. The red dot indicates the group mean. Abbreviations: ns = not significant, SD = standard deviation

A total of 18 patients completed the entire study assessment at all three timepoints. To assess the distribution of the data, Shapiro-Wilk test of normality was performed, observing normal distribution for HADS Anxiety summary score for entry and exit. However, at the follow-up the dataset differed significantly from normal distribution (entry p=0.12, exit p=0.34, follow-up p=0.04).

To account for the distribution of the data at different timepoints, t-tests on parametric data and Wilcoxon rank tests on non-parametric data were performed. The patients showed significant difference in their HADS Anxiety scores from exit to follow-up (p=0.027) (Figure 11). After adjustment for multiple comparison correction (Bonferroni) between respective timepoints, the patients showed no significant difference from exit to follow-up regarding HADS Anxiety (p=0.08).



Figure 11: t-tests and Wilcoxon rank tests for HADS Anxiety summary scores Boxplot showing the mean (horizontal line) and the box representing the 25th or 75th interquartile range, respective. The error bars represent the max or mind value, respectively. The red dot indicates the group mean. Abbreviations: ns = not significant, SD = standard deviation

For 18 patients, who completed the entire study assessment at all three timepoints, normal distribution for HADS Depression summary score was observed according to Shapiro-Wilk test of normality (entry p=0.24, exit p=0,11, follow-up p=0.62).

Differences between individual timepoints was analysed using t-test, adjusted for multiple comparison correction (Bonferroni). Patients' depression mean score significantly dropped from exit to follow-up (0.019), and again significantly increased from exit to follow-up (0.011), but they showed no significant difference from entry to follow-up (0.861) (Figure 12).



Figure 12: t-tests for HADS Depression summary scores

Boxplot showing the mean (horizontal line) and the box representing the 25th or 75th interquartile range, respective. The error bars represent the max or mind value, respectively. The red dot indicates the group mean. Abbreviations: ns = not significant, SD = standard deviation

3.2.5. Clinical symptoms

Clinical outcomes in n=35 patients at entry, n=34 patients at exit, and n=22 patients at followup were evaluated. One patient who was assessed at the entry timepoint did not take part in the exit assessment, while 13 patients who were evaluated at entry did not participate in the followup assessment.

Data was normally distributed. The mean S-FMDRS summary scores (SD) were 15.1 (\pm 7.3) at entry, 11.4 (\pm 7.3) at exit, and 10.1 (\pm 7.8) at the follow-up. There was a significant difference in the S-FMDRS total score between timepoints (*F*(2,88)=3.6, *P*=0.0134, (Figure 13).

A total of 21 patients completed the entire study assessment at all three timepoints. To evaluate the distribution of data, Shapiro-Wilk test of normality (entry p=0.15, exit p=0.35, follow-up p=0.09) was performed. Pairwise comparison on the data revealed a significant drop from entry to exit (p=0.001) and from entry to follow-up (p=0.003), however, no significant difference was observed between exit and follow-up (Figure 14). Analyses were corrected for multiple comparisons using Bonferroni correction.



Figure 13: Repeated ANOVA (factor timepoint) for S-FMDRS Boxplot showing the mean (horizontal line) and the box representing the 25th or 75th interquartile range, respective. The error bars represent the max or mind value, respectively. The red dot indicates the group mean. Abbreviations: ns = notsignificant, SD = standard deviation



Figure 14: t-tests and Wilcoxon rank tests for EQ VAS

Boxplot showing the mean (horizontal line) and the box representing the 25th or 75th interquartile range, respective. The error bars represent the max or mind value, respectively. The red dot indicates the group mean. Abbreviations: ns = not significant, SD = standard deviation

4. Discussion

4.1. Summary on Main Results

This study used PROMs and clinical outcome measures to assess whether the three weeks multidisciplinary inpatient treatment at the Psychosomatic Medicine at Inselspital Bern has a significant beneficial effect on subjective (QOL, social functioning, and well-being) and objective (symptoms severity) outcomes for FND patients.

Current data from an ongoing data collection show a significant improvement in clinical symptoms, but no clear significant improvements in PROMs in response to the three weeks multidisciplinary inpatient treatment.

4.1.1. Quality of life

The patients' QOL, as measured by the EQ-5D-5L index score as well as the EQ VAS for all 43 patients who participated in the questionnaire at any point of the study showed no significant improvement after the three weeks therapy at exit or at the three months follow-up compared to entry. However, looking at the patients for whom data was available at all three time points, there is a significant improvement in QOL, as measured by the EQ VAS, at exit compared to entry, but the improvement was not significant after adjusting for multiple comparison correction. As the reasons for missing data were unclear, the potential effect of improvement in QOL for patients who participated in all three assessments, compared to patients with missing data, cannot be explained. A possible reason could be that patients with poorer QOL have less energy or motivation to complete the questionnaires, or that due to physical limitations the entire set of questionnaires could not be completed. This could introduce a bias in the dataset and the results could potentially be weaker if data were available from all patients.

The EQ VAS assessment of current QOL on the 0-100 level appears to give a different picture of the change in QOL than the index score based on the five questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The patient's general QOL (measured by EQ VAS) seems to improve subjectively more than only in relation to the five scales, suggesting that other aspects might influence the patient's QOL stronger additional to the corresponding five criteria.

In previous literature, the outcomes and their interpretation are ambiguous and inconsistent. In a study by Nielsen et al., (2015), a five day physiotherapy program for functional (psychogenic) motor disorders resulted in a significant increase in the index score of 0.125 (CI=0.19, 0.06) from baseline/entry 0.35 (CI=0.27, 0.43) to three months follow-up 0.47 (CI=0.39, 0.55). In a randomized feasibility study comparing a specialized inpatient physiotherapy program to TAU

at a local physiotherapy service, the EQ-5D-5L utility scores were significantly higher in the intervention group (0.34 ± 0.03) compared to TAU (0.26 ± 0.04) at six months follow-up (Nielsen, Buszewicz, et al., 2017). An increase in the prevalence for level 1 (no problem) in all domains and a decrease in level 4 (severe problem) and 5 (extreme problem) between entry and six months follow-up could be shown in a study of a five weeks individualized multidisciplinary day-patient treatment program for FND, which included physiotherapy, occupational therapy, cognitive behavioral therapy (CBT), and neuropsychiatry. A similar increase in EQ-5D-5L index scores as well as EQ-VAS scores was shown between entry, exit and six months follow-up (Petrochilos et al., 2020). However, the effect size in the study was small and the differences were not significant. A large multicenter randomized control trial by Goldstein et al., (2020) reported a better health-related QOL on the EQ VAS for CBT plus standardized medical care compared to standardized medical care at twelve months follow-up (mean difference 6.16±4.68, p=0.010). On the other hand, the QOL measured by other questionnaires did not significantly differ between groups at twelve months follow-up. However, according to Gelauff & Stone, (2016) the measures for QOL were often poor at follow-up in large part of the studies.

4.1.2. General and psychosocial functioning

There was no significant difference in the WSAS score over all patients between entry (n=36), exit (n=21) and follow-up (n=20). Interpretation of the data is difficult since the patients measured at follow-up were not always the same patients that were measured at exit. However, as the scores measured were above 20 in all three timepoints, a high degree of impairment in patients must be assumed throughout the full assessment period.

Looking at the results for the patients (n=10) with data for all three timepoints, there is a significant reduction in impairment from entry to exit. The reduction in impairment seems to be stable from exit to three months follow-up, although there is no significant difference from entry to follow-up. Since the questionnaire refers, among other things, to the ability to work, household management and private leisure activities, a reduction in impairment from entry to exit might not directly be explained by means of the therapy but rather be given by the general setting, which is quite different in an inpatient stay than at home (i.e., no household management to do). For this reason, the change from entry to follow-up is a more relevant measure of impairment than the change from entry to exit, as it represents longterm sustainable changes in mental health.

In the five day physiotherapy program by Nielsen et al. (2015), the WSAS mean scores improved significantly from entry (24.2 \pm 8.0) to three months follow-up (21.0 \pm 7.2) (p<0.001) and from exit (23 \pm 7.6) to three months follow-up (21.0 \pm 7.2) (p=0.015), Another study

comparing an intensive inpatient physiotherapy program to TAU, which consisted of a referral to local physiotherapy service, showed no significant difference in WSAS scores between the program and TAU at six months follow-up adjusted for baseline difference (Nielsen, Buszewicz, et al., 2017).

Studies on psychoeducation also showed different results. Patients attending group psychoeducation sessions showed significant improvement on WSAS scores compared to the control group only receiving routine visits at three months follow-up (p=0.013), as well as at six months follow-up (p=0.038) (Chen et al., 2014). An observational study on manualized psychoeducation showed no significant difference in WSAS scores before (26 ± 17.9) and after (20.5 ± 14) treatment comparing WSAS scores (p=0.112) (Wiseman et al., 2016).

Goldstein et al. (2020) showed significant improvement in psychosocial functioning for CBT plus standardized medical care compared to standardized medical care alone at twelve months follow-up (mean difference 4.12 ± 2.23 , p<0.001).

However, interpretation of the results is difficult since evidence for the validity or reliability of either scale is not available in FND samples (Pick et al., 2020).

4.1.3. Psychological impairment

There was no significant difference in the HADS score neither for depression nor for anxiety in all patients between entry (n=42), exit (n=36) and follow-up (n=19). In the HADS, mean scores between 8-10 for each both scales indicate mild symptoms (Petermann, 2011). With the highest mean score was shown for anxiety at entry with 7.2 (\pm 4.6), the mean depression and anxiety scores were not in a clinically relevant range at any time.

Looking at the results for the patients (n=18) with data for all three timepoints, there was a significant increase in mean scores for anxiety from exit (4.33 ± 3.18) to follow-up (5.89 ± 3.18) (p=0.027). However, after adjusting for multiple comparison correction (Bonferroni) there was no significant difference in mean anxiety scores. Still, both mean anxiety scores are indicated as not clinically relevant. The mean depression score for patients with data for all time points (n=18) shows a significant (p=0.011) increase in depressive symptoms from exit (3.83 ± 3.03) to follow-up (5.89 ± 3.18), which also remains significant after multiple comparison correction. Nevertheless, the scores for depression are also below the clinically relevant cut-off.

In many other studies on treatment for FND patients, the mean HADS scores for depression and anxiety showed no significant improvement. An observational study on CBT-based group psychoeducation showed no significant improvement in depression mean scores (entry 8.6 ± 6.0 , exit 7.8 ± 5.0 , p=0.34) and anxiety mean scores (entry 9.1 ± 5.3 , exit 8.4 ± 5.0 , p=0.46) before and after therapy (Conwill et al., 2014). An RCT comparing CBT+TAU to TAU in an outpatient neuropsychiatric setting showed no significant group and time interactions for either HADS anxiety or depression mean scores at the end of the treatment or at six months follow-up compared to the start of the treatment (Goldstein et al., 2010). A later study from Goldstein et al. (2020) comparing CBT plus standardized medical care to only standardized medical care showed no significant differences in anxiety (p=0.069) and depression (p=0.099) scores between the groups at twelve months follow-up. The 5-day specialist physiotherapy program by Nielsen et al. (2015) did not result in significant change in HADS mean anxiety scores (entry 7.1±4.4, exit 6.1±4.7, follow-up 6.9±4.6, p=0.114) or HADS mean depression scores (entry 6.0 ± 3.9 , exit 5.3 ± 4.0 , follow-up 6.0 ± 4.6 , p=0.96) during and after treatment. A later study by Nielsen, Buszewicz, et al. (2017) compared a specialized inpatient physiotherapy program to TAU at a local physiotherapy service showed no significant differences between the two groups for HADS anxiety and depression mean scores at six months follow-up for either of the scores. Only two studies found significant improvements in HADS scores. An observational study with a specialist inpatient multidisciplinary rehabilitation found significant reduction (p=0.011) in HADS scores from entry to exit, but no significant difference from entry to 1-year follow-up (Demartini et al., 2014). In another observational study on CBT for FND patients with dissociative seizures, the HADS anxiety mean scores (pre-treatment 10.06±5.62, end-treatment 7.81, 5.52, 6-months follow-up 8.13±6.71) and depression mean scores (pre 6.75±3.55, end 4.63 ± 4.22 , 6-months follow-up 4.63 ± 5.08) decreased significantly before and after treatment (p<0.05) and the improvements stayed sustained at six months follow-up (Goldstein et al., 2004).

In all studies, the mean scores are in the range of mild symptoms or even below, which may explain why no significant results can be found. In addition, depression and anxiety may be concomitant symptoms that can also be lowered by reducing the other symptoms of FND.

4.1.4. Clinical symptoms

In contrast to the PROMs, a significant improvement has been detected in the clinical changes related to symptoms (measured with the S-FMDRS) in all patients between entry (n=35), exit (n=34) and follow-up (n=22), p=0.03. Symptoms were significantly reduced at exit (11.4 \pm 7.3) compared to entry (15.1 \pm 7.3) and were slightly reduced again at three months follow-up (10.1 \pm 7.8).

For the patients (n=21) with data for all three timepoints, the results were even stronger. There is a significant reduction in symptoms from entry (16.43 ± 7.50) to exit (10.86 ± 7.19) (p=0.001), as well as from entry to three months follow-up (9.86±7.9) (p=0.03), and remained significant after multiple comparison correction (Bonferroni).

The therapy seems to have a significant effect on the improvement of symptoms, which also remained three months after the end of the therapy.

This effect is consistent with recent literature. All the studies found in the scoping review showed an improvement in symptoms after therapy. Since only one treatment study with the S-FMDRS was found, treatment studies with the PMDRS were also included.

In the study by Schmidt et al. (2021), symptoms measured with the S-FMDRS were significantly reduced from entry=11 to exit=4 and five months follow-up=3 (p<0.001) after a multimodal inpatient treatment. A twelve week CBT treatment had a significant effect on the reduction of the symptoms from entry (34.3 ± 17.1) to exit (7.4 ± 10.8), (p<0.001) measured with the PMDRS (Espay et al., 2019).

A significant reduction in symptoms was also demonstrated in two one-week multidisciplinary inpatient treatment studies. Jacob et al. (2018) showed a significant improvement in symptoms in motor FND patients from entry (30 ± 11.8) to exit (12.3 ± 9.9) (p<0.01) and Faul et al. (2020) found a significant mean reduction from pre to post (17.1 ± 5.3) (p<0.0001), both measured with the PMDRS.

These results are in line with the therein reported findings in the Psychosomatic Medicine at Inselspital Bern. Although only one of the studies had a follow-up, the effects are comparable as in the therapy program investigated within the scope of this study.

Interpretation:

In general, it can be said that the clinical outcome measures do not coincide with the PROMs. Clinical outcomes may appear better from an objective perspective, but from the patient's subjective perspective the improvement in clinical outcomes does not translate to better QOL. This is also in line with a study on multidisciplinary inpatient treatment, the clinician-rated assessments were more sensitive to change over time, whereas patient-reported measures performed less well (Demartini et al., 2014). Further, a study by Ricciardi et al. (2015) shows that FND patients tend to overestimate their symptoms and their severity, compared to objective rating.

According to Gelauff & Stone (2016) significant improvement in symptoms, based on clinicians' rating was not always correlated with patients' wellbeing, measured by an improvement in QOL, and general and psychosocial functioning, and a reduction in psychological distress. This could be due to a different perception of the symptoms.

Jones et al. (2016) argued that a reduction of symptoms at follow-up may not be the only relevant measure to give a prognosis, and QOL improvement at follow-up provide a better indication for the long-term perspective of FND patients.

The fact that in this study the results of patients with a full data set for all three time points sometimes differed from those of patients with an incomplete data set and the outcomes were sometimes better for patients with a full data set, suggests that patients with a poorer outcome are less able to attend the interviews for the questionnaires. Perhaps they were unable to participate in the assessments at all three time points due to severe symptoms or poor well-being.

In summary, the assessment of the treatment effect in this study seem to differ in terms of the clinicians' perspective versus the patients' perspective. It is likely that clinicians' expectations are different from patients' expectations. While patients may undergo treatment expecting a cure or an improvement in well-being, clinicians may judge the effects of treatment on the basis of clinical symptoms such as severity or duration. It can be said that therapy is mainly about how patients feel and how they cope with the disease. It is possible that the subjective perspective should be weighted higher than the clinical measures when assessing the success of therapy.

4.2. Limitations and future outlook

Several limitations need to be addressed concerning this study. Firstly, the sample size for analyzing data from patients with a full dataset at all three time points is quite small, especially for the WSAS (n=10) and EQ-5D-5L (n=13). As the data collection was designed for clinical aspects and not for research purposes and is still going on, there are limitations to the quality of the data. Data collection for PROMs was executed differently for follow-up than for entry and exit and no appointment was scheduled to assess the follow-up data. At the follow-up patients could not ask questions and may have completed the questionnaires in a different order or not at all. This led to an incomplete data set and thus to a rather small sample size for patients with a full dataset at all timepoints. In addition, the method for data collection could led to a selection bias that patients with more severe symptoms and higher impairment were not included in the analysis due to inability to complete the full assessment. The analysis could be repeated with a larger power at a later timepoint when additional patients will be treated.

As for all studies with questionnaires, one limitation is that it represents momentary glimpses that can be influenced by various aspects. The EQ-5D-5L refers to the state "today" and outcomes could be different the day before or the day after. This also applies for symptom

severity measured by the S-FMDRS. The symptoms of FND can vary over a short period of time and lead to different results in clinical examination.

This study is also not representative of all FND inpatients, as informed consent was required for the analysis of patient data. Currently, in contrast to the inpatients, no routine data collection has been performed on the outpatients of FND, which could be used as a control group. It is important to consider that patients with more severe symptoms were more often treated in an inpatient setting, whereas patients with less severe symptoms receive outpatient treatment. Consequently, it is plausible that substantial improvement in outcomes may only become apparent at a later stage. Moreover, comorbidities were not considered in the analysis and may have influenced the outcomes.

Another aspect is that the due to the small sample size, differences between subtypes of FND have not been addressed. It could be that treatment outcomes differ, for example, in patients with non-epileptic seizures compared to patients with functional movement disorders. For future studies and with a larger sample size, differences between FND subtypes should be examined.

Furthermore, patients' individual therapy after discharge was recorded but not included in the analyses. Outpatient therapy could certainly influence the development of the disease and the outcomes at follow-up. Further studies should consider this aspect within their analyses.

5. Conclusions

This study confirms that the three weeks multidisciplinary inpatient treatment at the Psychosomatic Medicine at Inselspital Bern could significantly reduce clinical symptoms for FND patients. However, subjective outcome measures reported by patients did not show a corresponding effect in QOL, well-being and social functioning. This might have been due to low test power, an inaccurate selection of questionnaires, or because the treatment does not influence the perceived QOL, well-being and social functioning. Further studies with a bigger sample size, analysis of other PROMs, and comparison to the currently running outpatient treatment at the Psychosomatic Medicine at Inselspital Bern, should examine the effect of the three weeks inpatient treatment in regard to different outcome measures.

6. Literature

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7. Appendix

Appendix 1: EQ-5D-5L

Anleitung: Bitte geben Sie an, welche Aussagen Ihren heutigen Gesundheitszustand am besten beschreiben, indem Sie ein Kreuz in ein Kästchen jeder Gruppe machen.

Beweglichkeit/Mobilität

- □ Ich habe keine Probleme herumzugehen
- □ Ich habe leichte Probleme herumzugehen
- □ Ich habe mässige Probleme herumzugehen
- □ Ich habe grosse Probleme herumzugehen
- □ Ich bin nicht in der Lage herumzugehen

Für sich selbst sorgen

- □ Ich habe keine Probleme, mich selbst zu waschen oder anzuziehen
- □ Ich habe leichte Probleme, mich selbst zu waschen oder mich anzuziehen
- **I**ch habe mässige Probleme, mich selbst zu waschen oder mich anzuziehen
- □ Ich habe grosse Probleme, mich selbst zu waschen oder mich anzuziehen
- **I**ch bin nicht in der Lage, mich selbst zu waschen oder anzuziehen

Allgemeine Tätigkeiten (z.B. Arbeit, Studium, Hausarbeit, Familien- oder Freizeitaktivitäten)

- **I**ch habe keine Probleme, meinen alltäglichen Tätigkeiten nachzugehen
- Lich habe leichte Probleme, meinen alltäglichen Tätigkeiten nachzugehen
- Lich habe mässige Probleme, meinen alltäglichen Tätigkeiten nachzugehen
- **I**ch habe grosse Probleme, meinen alltäglichen Tätigkeiten nachzugehen
- **I**ch bin nicht in der Lage, meinen alltäglichen Tätigkeiten nachzugehen

Schmerzen/Körperliche Beschwerden

- □ Ich habe keine Schmerzen oder Beschwerden
- □ Ich habe leichte Schmerzen oder Beschwerden
- □ Ich habe mässige Schmerzen oder Beschwerden
- □ Ich habe grosse Schmerzen oder Beschwerden
- □ Ich habe extreme Schmerzen oder Beschwerden

Angst/Niedergeschlagenheit

- □ Ich bin nicht ängstlich oder deprimiert
- □ Ich bin ein wenig ängstlich oder deprimiert
- □ Ich bin mässig ängstlich oder deprimiert
- □ Ich bin sehr ängstlich oder deprimiert
- □ Ich bin extrem ängstlich oder deprimiert

Um Sie bei der Einschätzung, wie gut oder wie schlecht Ihr Gesundheitszustand ist zu unterstützen, haben wir eine Skala gezeichnet ähnlich einem Thermometer. Der beste denkbare Gesundheitszustand ist mit einer «100» gekennzeichnet, der schlechteste mit «0».

Wir möchten Sie bitten, auf dieser Skala zu kennzeichnen, wie gut oder schlecht Ihrer Ansicht nach Ihr persönlicher Gesundheitszustand heute ist. Bitte verbinden Sie dazu den untenstehenden Kasten mit dem Punkt auf der Skala, der Ihren heutigen Gesundheitszustand am besten wiedergibt.



Appendix 2: WSAS

Bewerten Sie die folgenden Fragen auf einer Skala von 0 bis 8.

0 bedeutet überhaupt keine Einschränkung und 8 steht für eine sehr starke Einschränkung.

	Überhaupt keine					Sehr starke			
	Einse	Einschränkung				Einschränkung			
	0	1	2	3	4	5	6	7	8
 Aufgrund meiner Erkrankung¹ bin ich in meiner Arbeitsfähigkeit eingeschränkt. 									
2. Aufgrund meiner Erkrankung* bin ich in meiner Haushaltsführung eingeschränkt (putzen, aufräumen, einkaufen, kochen, zum Haus und zu den Kindern schauen, Rechnungen bezahlen).									
3. Aufgrund meiner Erkrankung* bin ich in meinen Freizeitaktivitäten eingeschränkt (mit anderen Menschen, z.B. auf Parties, in Bars, Clubs, beim Ausgehen, bei Besuchen, Verabredungen, Unterhaltung zuhause).									
 4. Aufgrund meiner Erkrankung* bin ich in meinen privaten Freizeitaktivitäten eingeschränkt (Freizeitaktivitäten alleine, z.B. lesen, Gartenarbeit, sammeln, nähen, alleine spazieren). 									
5. Aufgrund meiner Erkrankung* bin ich im Bilden und Aufrechterhalten von engen Beziehungen – inklusiven den Menschen, mit denen ich zusammenlebe – eingeschränkt.									

¹ Erkrankung, wegen derer Patient:in stationär behandelt wird/wurde

Wir bitten Sie jede Frage zu beantworten, und zwar so, wie es für Sie persönlich <u>in der letzten</u> <u>Woche</u> am ehesten zutraf. Machen Sie bitte nur ein Kreuz pro Frage und lassen Sie bitte keine Frage aus! Überlegen Sie bitte nicht lange, sondern wählen Sie die Antwort aus, die Ihnen auf Anhieb am zutreffendsten erscheint! Alle Ihre Antworten unterliegen der ärztlichen Schweigepflicht.

1. Ich fühle mich angespannt oder überreizt
0. meistens
1. oft
2. von Zeit zu Zeit / gelegentlich
3. überhaupt nicht
2. Ich kann mich heute noch so freuen wie früher
0. ganz genau so sehr
1. nicht ganz so sehr
2. nur noch ein wenig
3. kaum oder gar nicht
3. Mich überkommt eine ängstliche Vorahnung, dass etwas Schreckliches passieren
könnte
0. ja, sehr stark
1. ja, aber nicht allzu stark
2. etwas, aber es macht mir keine Sorgen
3. überhaupt nicht
4. Ich kann lachen und die lustige Seite der Dinge sehen
0. ja, so viel wie immer
1. nicht mehr ganz so viel
2. inzwischen viel weniger
3. überhaupt nicht
5. Mir gehen beunruhigende Gedanken durch den Kopf
0. einen Grossteil der Zeit
1. verhältnismässig oft
2. von Zeit zu Zeit, aber nicht allzu oft
3. nur gelegentlich / nie
6. Ich fühle mich glücklich
0. überhaupt nicht
1. selten
2. manchmal
3. meistens

7. Ich kann behaglich dasitzen und mich entspannen
0. ja, natürlich
1. gewöhnlich schon
2. nicht oft
3. überhaupt nicht
8. Ich fühle mich in meinen Aktivitäten gebremst
0. fast immer
1. sehr oft
2. manchmal
3. überhaupt nicht
9. Ich habe manchmal ein ängstliches Gefühl in der Magengegend
0. überhaupt nicht
1. gelegentlich
2. ziemlich oft
3. sehr oft
10. Ich habe das Interesse an meiner äusseren Erscheinung verloren
0. ja, stimmt genau
1. ich kümmere mich nicht so sehr darum, wie ich sollte
2. möglicherweise kümmere ich mich zu wenig darum
3. ich kümmere mich so viel darum wie immer
11. Ich fühle mich rastlos, muss immer in Bewegung sein
0. ja, tatsächlich sehr
1. ziemlich
2. nicht sehr
3. überhaupt nicht
12. Ich blicke mit Freude in die Zukunft
0. ja, sehr
1. eher weniger als früher
2. viel weniger als früher
3. kaum bis gar nicht
13. Mich überkommt plötzlich ein panikartiger Zustand
0. ja, tatsächlich sehr oft
1. ziemlich oft
2. nicht sehr oft
3. überhaupt nicht
14. Ich kann mich an einem guten Buch, einer Radio- oder Fernsehsendung freuen
0. oft
1. manchmal
2. eher selten

3. sehr selten

Appendix 4: S-FMDRS

The Simplified Functional Movement Disorders Rating Scale (S-FMDRS).

UL, upper limb; LL, lower limb. (Nielsen, Ricciardi, et al., 2017)

Regions	Severity	Duration	Total	Scoring			
Face & tongue					Severity	Duration	
Head & neck				0	None	None of the time	
Left UL & shoulder girdle				1	Mild	Occasionally	
Right UL & shoulder girdle				2	Moderate	Frequent	
Trunk & abdomen				3	Severe	Constant	
Left LL							
R LL							
Function							
Gait							
Speech							
		TOTAL					