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Successful long-term management of spasticity in patients with multiple sclerosis using a software application (APP): A pilot study

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ABSTRACT

Background: Spasticity is a very common syndrome in patients with multiple sclerosis (pwMS), but available treatments lead to sufficient symptom control only in one third.
Objective: To investigate the impact of an individualized training program on improving spasticity in a prospective pilot trial in pwMS suffering from moderate spasticity (defined as ≥ 4 on a normative rating scale; NRS).
Methods: PwMS were familiarized with predefined exercises targeting spasticity while undergoing inpatient rehabilitation (IR). After IR, 20 pwMS were 1:1 randomized either to a newly designed APP-based home therapy program providing suitable exercises on a daily basis or to a paper-based home therapy program for 3 months. At month 3, all patients received the APP-based home program for another 3 months. Degree of spasticity was rated on the NRS.
Results: Undergoing inpatient rehabilitation for a mean of 32 days led to a significant reduction in spasticity in pwMS ($p = 0.00$). Further self-training with the APP-based home program for 3 months led to 1.2 lower mean NRS as compared to training with the conventional paper-based program ($p = 0.09$). Spasticity was found to be on low levels again in both groups after 6 months.
Conclusion: In pwMS, an individually tailored anti-spasticity program delivered by a software APP is a feasible tool for increasing long-term adherence to self-training thereby positively impacting spasticity in pwMS.

1. Introduction

Spasticity is a disabling syndrome of multiple sclerosis (MS) affecting up to 84% of patients to various degrees (Rizzo et al., 2004). It contributes to overall disability and reduced mobility, is associated with poor postural control, painful spasms and sleep disturbances and can cause severe complications such as contractures (Beard et al., 2003; Rizzo et al., 2004). On the other hand spasticity can also be perceived as helpful by patients, as they are able to use stiffness when walking or transferring. Measuring spasticity is difficult and although the Ashworth scale is the most widely used instrument (Bohannon and Smith, 1987), there are strong concerns that it is unreliable and insensitive by focussing only on passive resistance to movement and not considering other aspects of spasticity (Pandyan et al., 1999). Recently, a numeric rating scale (NRS) for spasticity has been validated in patients with MS (pwMS), levels of clinically important differences have been defined and the scale was recommended as a patient-centred outcome measure that reflects the impact of spasticity in an individual patient (Farrar et al., 2008).

Managing spasticity requires striking a balance between maximizing the beneficial effects whilst minimizing negative aspects of treatment. Current pharmacological treatments for spasticity in MS include baclofen, tizanidine, gabapentin, diazepam, dantrolene and nabiximol (Otero-Romero et al., 2016). All of them are associated with dose-limiting adverse affects and despite their wide-spread use, many pwMS continue to experience moderate to severe spasticity (Collongues et al., 2013). Non-pharmacological interventions, either isolated or in combination with pharmacological treatments have proven their efficacy and are still the mainstay in the management of spasticity (Amatya et al., 2013). Though spasticity is a chronic problem that often progresses with the disease (Beard et al., 2003), interventions should be performed on a daily and lifelong basis. However, major barriers including financial issues, limited time resources, and the lack of clear professional instructions on techniques, intensity and duration of

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therapy often prevent the implementation of interventions in everyday life of pwMS (Asano et al., 2013).

Recently, new technologies including mobile software applications (APP) have entered various medical fields. The fact that up to 94% of pwMS of a Western population have been reported to have internet access also makes them potentially APP-users (Haase et al., 2012). Despite their great benefits, APPs also harbour limitations: APPs generally lack evaluation in terms of safety or even efficacy.

The present pilot study investigated the feasibility of an individually tailored anti-spasticity program, which is delivered by a specifically designed "MS-spasticity APP" and its effect on long-term spasticity management in pwMS, thereby also providing data for sample size estimation for a confirmative study.

2. Material and methods

2.1. Study design and patient recruitment

The study was approved by the ethics committee of the Medical University Innsbruck, Austria (study-nr. AN4739 314/4.10) and all participants provided written informed consent.

Study participants were recruited prospectively at the Clinic for Neurological Rehabilitation Münster, Austria, between May 2013 and August 2015. Key eligibility criteria included diagnosis of MS of any disease subtype and a 6-month history of lower limb spasticity due to MS (Polman et al., 2011). Severity of spasticity was scored by study participants on the 0–10 numeric rating scale (NRS)(Farrar et al., 2008). A mean daily NRS score of ≥ 4, which equals moderate spasticity, on three consecutive days prior to inpatient rehabilitation (IR) was chosen as minimum threshold. Patients underwent neurological IR for a minimum of 29 days; they received 38 individual physiotherapy, occupational and/or speech therapy sessions, targeting their primary rehabilitation goals, and a minimum of 38 group therapy sessions, each lasting 25 min. Changes in the anti-spasticity drug treatment were only permitted within 3 days after start of the IR. Key exclusion criteria were a score on the expanded disability status scale (EDSS) > 6.5, a relapse 30 days and therapy with botulinum toxin on lower limbs 90 days prior to study inclusion, concomitant diseases associated with spasticity or severe cognitive impairment (mini mental status examination < 27). Study participants were clinically assessed during IR, and 12 and 24 weeks thereafter.

2.2. Intervention program

An exercise program was designed to be performable within the kitchen or living room of everyone's home by using minimal equipment (e.g. chair, table, books). Individual disability and spasticity was acknowledged by different body positions (sitting, standing, kneeling or lying). In total a pool of 85 exercises was set up with focus on movement, strengthening and coordination of lower limbs and trunk and a video sequence showing a physiotherapist performing the exercise was made for each of them. Exercises were assigned to regions foot, knee, hip and trunk resulting in a total of 10 possible categories (Table 1).

The daily program was intended to consist of two blocks, each lasting 15 min. A block typically started with a movement (5 min), followed by a strengthening (5 min) and ending up with a coordinative task of either regions foot/knee or hip/trunk.

During IR, the treating physiotherapist selected as many suitable exercises as possible, but at least one out of each category. All participants were familiarized with exercises during IR and instructed to perform movements slowly and in full range of motion to mobilize joints and to stretch muscles in a dynamic way. Strengthening exercises were assigned to be held in end position shortly and coordination exercises had to be performed slowly (Fig. 1).

2.3. Individually tailored APP-based home therapy

An "MS-spasticity APP" was designed (MP2 IT Solutions GmbH, Vienna, Austria) to be run on a tablet (Samsung Galaxy Note 10.1), which was provided to study participants. Selected exercises were presented as short video sequences (five minutes each) with previews giving information on the type of exercise and which equipment would be needed (chair, table, book), followed by a countdown. Six exercises out of 10 possible categories, separated into 2 blocks, were presented daily, on 6 consecutive days of the week. To account for active participation, participants had to complete each session by tapping a button in the APP. Fast-forwarding or skipping exercises was not enabled by the APP. Exercises were rated as completed only if all 3 exercises of a block were run. At 7 p.m. an automatic email reminder would encourage participants to complete their exercises if the APP had not yet registered any activity for that particular day. Pre-formulated slogans and reminders had been implemented during software development to praise participants for regular exercise and motivate them should their completion rate fall below 80%. An integrated email account served as an additional possibility to contact the study team in case of questions. NRS spasticity and patient reported outcomes (PROs) were requested via "MS-spasticity APP" at week 12 and 24.

2.4. Individually tailored conventional home therapy

Providing a home therapy program is considered good clinical practice in neurological rehabilitation and was therefore chosen as control intervention. Study participants were provided with screenshots of selected exercises and PROs on hard copy (paper) and instructed to perform these exercises for a minimum of half an hour on a daily basis. After 12 weeks, study participants again received instruction in how to correctly perform the exercises by a physiotherapist and were also provided with a tablet and the "MS-spasticity APP" for another 12 weeks.

Table 1
Exercise program with different categories of interventions and a representative example.

#	Intervention	Example
1	movement foot with mobilisation of metatarsophalangeal and upper ankle joint	heel raising in reversed sitting position
2	strengthening foot (triceps surae)	heel raising in standing position, stabilising with hands on a table
3	movement with mobilisation knee joint	alternate straightening and bending knees, upper body stabilised on kitchen unit
4	strengthening knee (quadriceps femoris)	mini wall squats, pelvis stabilised against the wall
5	coordination movements of foot/knee	bending knees and trunk forward, then extending body and raising heels
6	movement with mobilisation of hip joint	standing close beside a wall, lifting unilateral knee then straightening leg backwards
7	strengthening hip muscles (flexor, extensor, abductor, external rotator)	lifting of straightened leg to the side in standing position, stabilising with hands on a table
8	movements with mobilisation of trunk	tilting pelvis in reversed sitting position
9	strengthening trunk (abdominal and back muscles)	push ups against kitchen unit
10	coordination movements of hip/trunk	Putting arm and contralateral knee together, then straightening arm and leg in all four positions

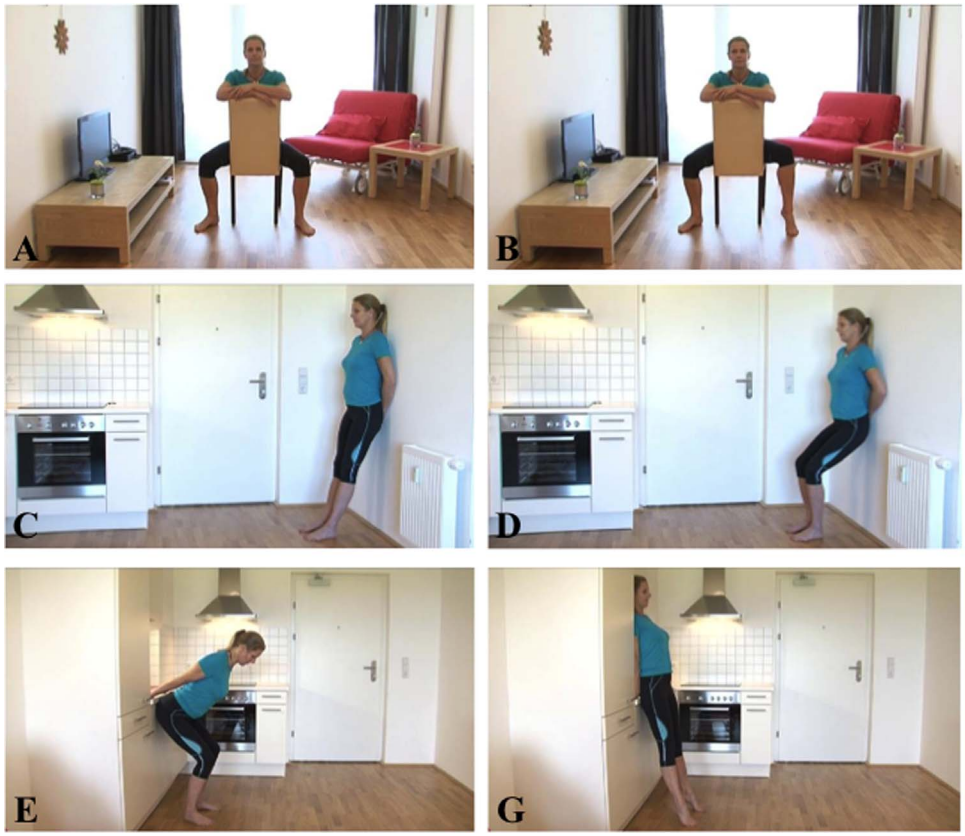

Fig. 1. Example of one block of exercises showing starting (A) and end position (B) of raising heels in reversed sitting position (category movement foot), starting (C) and end position (D) of mini wall squats (category strengthening knee) and starting (E) and end position (F) of bending knees and trunk forwards followed by extending body and raising heels (category coordination foot/knee).

2.5. Randomization

An automated biased coin algorithm with blocks of 4 was used to randomize participants to either APP-based home therapy program for 6 months or conventional, paper-based home therapy program for 3 months, followed by APP-based home therapy program for 3 additional months on the last day of IR (Vickers et al., 2006).

2.6. Outcome measures

2.6.1. Spasticity

A 0–10 NRS (0, indicating no spasticity and 10 severe spasticity) was used to measure the level of spasticity experienced by the study participants. To account for inter-day variability in spasticity, mean NRS of at least three consecutive days was used for the analysis (Farrar et al., 2008). Passive resistance to movement on lower extremities was scored using the modified Ashworth scale (MAS), which was rated by two experienced neurologists at baseline, week 12 and 24 (Bohannon and Smith, 1987). A mean score for each leg was calculated out of the following muscle groups: iliopsoas, adductors, quadriceps femoris, biceps femoris and triceps surae.

2.6.2. Lower extremities function

Strength in lower extremities was measured using the Motricity Index (MI), a validated measure of muscle power assessing hip flexion, knee extension and ankle dorsiflexion (Demeurisse et al., 1980). Ambulation was scored using the timed 25-foot walk (T25FW)(www.nationalmssociety.or, 2016).

2.6.3. Patient-based outcome measures

Self-rating scales were used to assess health related quality of life (HRQoL)(Morfeld et al., 2011), pain (11-point normative rating scale with 0 indicating no pain and 10 indicating severe pain), anxiety and depression (Hospital anxiety and depression scale; cut-off value used for abnormal testing > 7)(Herrmann-Lingen et al., 2011) and fatigue (cut-off values indicating physical fatigue or cognitive fatigue > 16 or > 17 respectively, indicating any fatigue > 32)(Flachenecker et al., 2006).

2.7. Statistical analysis

Variables are presented as median value and interquartile range or mean with 95% confidence intervals (CI). Differences between patient groups were compared at baseline using Fisher's exact test or independent *t*-test and two-way ANOVA at month 3 for interaction of treatment and time respectively. Significance was based on a p-value of < 0.05. Data was analysed using SPSS 20 (SPSS Inc, Chicago, IL, USA).

3. Results

3.1. Baseline and demographic data

A total of 97 pwMS consecutively referred to IR was screened for spasticity before starting IR. 72 individuals (71%) had to be excluded since they did not experience a minimum spasticity level of ≥ 4 ($n = 64$), had an EDSS > 6.5 ($n = 4$), severe cognitive impairment ($n = 4$), or refused to continue with further home training program due to logistic reasons ($n = 5$; Fig. 2). In total, 20 pwMS were familiarized with individually tailored exercises targeting spasticity while undergoing IR. In comparison to pre-rehabilitation (mean 5.7; STD 1.2), pwMS exhibited a mean reduction of 38% in subjectively perceived spasticity at the end of the stay (mean 2.9; STD 1.6; $p = 0.00$). PwMS were randomized at the last day of IR to “MS-spasticity APP” ($n = 10$) or to a paper-based home therapy program for 3 months ($n = 10$). There were no statistically significant differences in demographic and clinical data between subjects in both groups at baseline (Table 2).

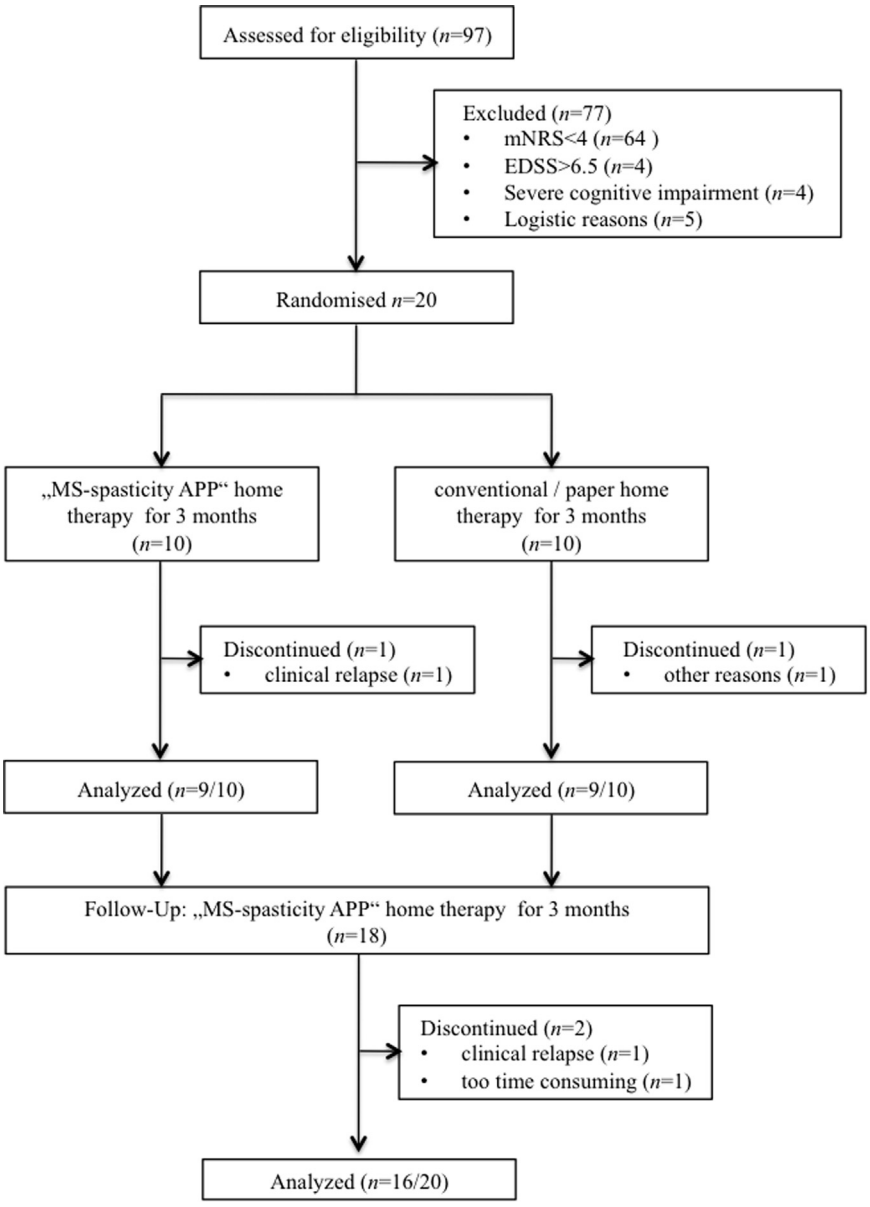

Fig. 2. Study flow chart.

Table 2
Baseline characteristics of study population.

Subject characteristics	"MS-spasticity APP"	Conventional therapy	*P*-value
Gender (females; males)	5; 5	4; 6	0.999[a]
Age in years[b]	46.6 (43.2–50.1)	50.5 (44.6–56.5)	0.217[c]
Disease duration in years[b]	12.6 (8.8–16.5)	16.3 (10.6–22.0)	0.325[c]
Expanded disability status scale[b]	4.2 (3.1–5.3)	5.4 (4.2–6.5)	0.099[c]
MS-subtype (relapsing; progressive)	2; 8	1; 9	0.999[a]
Antispastic drug treatment[d]	7	9	0.582[a]

[a] Fisher's exact test.
[b] mean (95% confidence interval).
[c] independent *t*-test.
[d] including baclofen and tizanidin.

3.2. Feasibility

As a measure of feasibility, we analysed MS patient dropout rates in the two groups. 18 patients completed the first 12-week self-training protocol. Reasons for discontinuation were clinical relapse ($n = 1$) in the "MS-spasticity APP" group and personal reasons ($n = 1$) in the conventional, paper-based group. No side effects attributable to the interventions were reported for either treated arm indicating that both interventions are feasible in pwMS with moderate disability (mean EDSS 4.8). Further, a completion rate of 80% of exercises was achieved when exercising with the "MS-spasticity APP".

3.3. Level of spasticity after 12 weeks of self-training protocol

Eight pwMS in the conventional group showed a worsening in mean NRS after 3 months of home training, whereas 5 pwMS in the "MS-spasticity APP" group remained stable or exhibited lower spasticity as measured with the NRS. These findings led to a 1.2 lower NRS in the "MS-spasticity APP" group at week 12 ($p = 0.09$; Table 3).

3.4. Secondary outcome parameters

In contrast to NRS, MAS scores for both legs did not change significantly between the "MS-spasticity APP" and the control group. Strength in lower extremities (MI) and ambulation (T25FW) were stable

Table 3
NRS spasticity on individual and group level.

	NRS spasticity			NRS spasticity	
Group #	Baseline	Month 3	group #	Baseline	Month 3
"APP 1"	1.0 (0.6)	1.3 (0.0)	*Control 1*	2.0 (0.0)	na
"APP 2"	3.3 (0.6)	3.3 (0.5)	*Control 2*	0.3 (0.6)	2.3 (1.1)
"APP 3"	3.3 (0.6)	2.6 (1.2)	*Control 3*	5.3 (0.6)	6.3 (0.6)
"APP 4"	4.3 (0.6)	3.0 (0.0)	*Control 4*	2.7 (1.2)	3.7 (0.8)
"APP 5"	3.3 (0.6)	na	*Control 5*	3.0 (0.0)	3.0 (1.0)
"APP 6"	4.3 (1.0)	4.0 (0.0)	*Control 6*	2.0 (0.0)	3.3 (0.4)
"APP 7"	4.0 (0.6)	4.3 (0.0)	*Control 7*	3.3 (0.6)	5.0 (0.0)
"APP 8"	2.7 (0.5)	3.3 (0.6)	*Control 8*	2.3 (0.6)	3.7 (0.6)
"APP 9"	2.7 (0.5)	2.7 (0.0)	*Control 9*	3.3 (0.6)	5.0 (0.0)
"APP 10"	0.3 (0.0)	2.0 (0.0)	*Control 10*	4.0 (1.0)	5.3 (0.5)
	*2. 9 (1.3)**	*3.0 (0.9)**		*2.8 (1.3)**	*4.2 (1.2)**

Na = not applicable due to drop out. NRS spasticity is given as mean (standard deviation) of at least three consecutive daily ratings in the week prior to randomization (baseline) and the week prior to month 3.

* refers to mean (standard deviation) per group. P-value 0.094 for interaction of treatment and time.

throughout the study period in both groups. No side effects attributable to the interventions were reported for either treated arm and none of the interventions was associated with a decrease in HRQoL or an increase in fatigue or pain. None of the participants exhibited signs of anxiety or depression before or throughout the study (Table 4).

3.5. Follow-up

After 12 weeks, also the control group received the "MS-spasticity APP". Two out of 18 participants did not complete the second 12-week self-training protocol. Reasons for discontinuation were clinical relapse ($n = 1$) and a too time consuming protocol ($n = 1$). Exercising with the "MS-spasticity APP" was associated with a decrease in mean NRS in all participants formerly training with the paper-based program at month 6. Two pwMS, who had already been exercising with the "MS-spasticity APP" for the previous three month, exhibited further improvement in terms of spasticity after the follow-up period. At the end of the intervention, mean levels of spasticity were overall lower than at the time of randomization (mean NRS 2.5; STD 1.7).

3.6. Pharmacological anti-spasticity treatment

12 pwMS were already on anti-spasticity treatment prior to IR. Anti-spasticity treatment was initiated (n = 4) or dosage moderately increased (n = 4) in 8 pwMS within the first 3 days of IR. At randomization, the mean dosage of baclofen was 27.8 mg (STD 31.6) and the mean dosage of tizanidin 4.8 mg (STD 5.5) in the "MS spasticity APP" group as compared to 29.7 mg (STD 21.4) baclofen and 7.1 mg (STD 5.6) tizanidin in the control group. One pwMS in each group received both drugs. There was no correlation between the decrease in NRS and the initiation or augmentation of the anti-spasticity drug dosage.

3.7. Sample size estimation for a confirmative study

Mean NRS values differ by 1.2 between the two intervention groups in our pilot study. Given a standard deviation of 1.3, a drop-out rate of 10%, a power of 80% and a two-sided significance level of 5%, we estimate that 50 patients in each group will be required in a confirmative study to detect a difference in the proportion of patients demonstrating long-term clinical benefit in terms of subjectively perceived spasticity using the "MS spasticity APP".

4. Discussion

Undergoing IR led to a significant reduction in subjectively perceived spasticity in our cohort of pwMS. Other than the MAS, the NRS represents a validated and recommended patient-centred self-reported outcome measure that mirrors everyday clinical practice and offers the possibility to share decision-making on spasticity treatment with the patient (Farrar et al., 2008; Gold and Oreja-Guevara, 2013). A 20% improvement in the subject-reported severity of spasticity has been reported to be the minimum clinically important difference, an improvement of 30% to have "much improved" (Farrar et al., 2008). Consequently the finding of a mean reduction of 38% in our cohort underlines the benefit of a tailored, IR program.

A key aspect in successful long-term management of a chronic problem like spasticity is the regular performance of exercises on an individual and self responsible basis also after a supervised IR program. Previous studies have already highlighted major barriers for the consequent implementation of exercises in everyday life of pwMS: financial

Table 4
Secondary outcome measures for both groups.

	Baseline		Month 3		
	"APP"	Control	"APP"	Control	p-value
Data available from	10	10	9	9	
Modified Ashworth scale lower extremities[a]					
left	1.8 (1.2)	1.5 (0.8)	1.3 (0.9)	1.5 (1.0)	0.443
right	1.9 (1.4)	1.7 (0.9)	1.0 (1.3)	2.0 (1.0)	0.127
Motricity index lower extremities (0–100)					
left	78.8 (21.1)	78.0 (9.5)	85.1 (20.1)	76.5 (20.8)	0.524
right	78.7 (20.8)	83.6 (17.9)	83.8 (14.0)	80.2 (12.4)	0.438
Timed 25-foot walk (seconds)	6.7 (2.7)	8.9 (3.6)	6.5 (1.5)	10.0 (4.3)	0.529
Quality of life (0–100)[b]					
physical health	37.8 (8.5)	37.8 (4.3)	36.4 (8.0)	37.4 (5.6)	0.825
mental health	51.6 (9.1)	52.6 (10.4)	48.1 (12.7)	48.8 (10.8)	0.966
Visual analogue scale pain (0–10)	1.6 (1.3)	0.8 (0.8)	2.8 (1.7)	3.4 (2.6)	0.219
Anxiety[c]	2.4 (3.4)	2.9 (2.4)	3.3 (2.9)	2.4 (2.1)	0.442
Depression[c]	2.5 (3.5)	4.5 (3.8)	4.8 (4.4)	4.9 (4.4)	0.474
Fatigue[d]					
physical	12.0 (4.9)	13.5 (6.8)	13.3 (4.9)	16.3 (6.3)	0.690
cognitive	8.2 (6.2)	7.3 (8.7)	10.3 (5.1)	4.9 (6.7)	0.312

Values are given as mean (standard deviation). Data were analysed using two-way ANOVA and p-values are given for interaction of treatment and time.

[a] Mean score of following muscle groups: iliopsoas, adductors, quadriceps femoris, biceps femoris and triceps surae. Timed 25-foot walk when performable within 180 s.[15].

[b] evaluated using the 36-item short form health survey (Morfeld et al., 2011).

[c] evaluated using the hospitality anxiety and depression scale with values > 7 indicating clinical relevant anxiety or depression (Herrmann-Lingen et al., 2011).

[d] evaluated using the Würzburger Fatigue Scale with values > 16 or > 17 indicating significant physical or cognitive fatigue respectively (Flachenecker et al., 2006).

issues, limited time resources, and the lack of clear professional instructions on techniques, intensity and duration of therapy (Asano et al., 2013). The present study aimed to overcome these barriers using an innovative strategy that provides pwMS with an individualized therapy program that is already familiar to them on the one hand, though exercises were selected by the treating physiotherapist according to the individual level of spasticity and pwMS were instructed in correct performance already during IR. On the other hand, the combination of detailed and visualized instructions, reminder functions and encouraging slogans mediated by the "MS-spasticity APP" should increase adherence to regular performance of exercises. And indeed, 80% of pwMS were able to engage regularly in the self-administered "MS-spasticity APP" program for half an hour daily for a period of 24 weeks in our pilot study, which is to our knowledge the longest treatment period that has been investigated in this context so far (Amatya et al., 2013). Of note is that the investigated cohort represents a typical MS population suffering from moderate to severe spasticity with progressive disease courses (80%) and an advanced disability status (mean EDSS 4.8) being predominant. Together with the high acceptance rate, the lack of side effects, the good tolerability we believe that the "MS-spasticity APP" offers a feasible and easy to handle tool for encouraging pwMS to perform exercises targeted against spasticity in a regular manner.

Although the present study was designed as an explorative pilot trial providing data for sample size estimation for a confirmative study, the "MS-spasticity APP" group already showed a statistical trend towards lower NRS values after 12 weeks of treatment as compared to the control group; notably, the control group was an interventional group, that was familiarized with the same specific interventions prior to randomization and was provided with the same instructions for further self-training, but on a paper basis. Moreover, the finding of further improvement in some pwMS in the "MS-spasticity APP" group even after IR and an improvement of all pwMS who received "MS-spasticity APP" after 12 weeks of paper-based home therapy is encouraging. Although it is very preliminary to draw any conclusions from our pilot study in terms of efficacy we think that the "MS spasticity APP" is a very feasible tool to maintain low-level spasticity in selected pwMS also in the long run, after an initial loss of more than a third in subjectively perceived spasticity by an intensive, IR program.

Change in anti-spasticity drug treatment can be a confounder in our study. To limit the potential influence of any anti-spasticity drug treatment on the reduction of spasticity, a change in medication was only allowed within the first 3 days IR, but not thereafter. Anti-spasticity drug treatment was initiated or dosage increased in 8 pwMS. However, this increase in dosage was overall only moderate and statistically not related to the decrease of subjectively perceived spasticity. Consequently, the change in anti-spasticity drug treatment is likely to have only a minor impact on the overall improvement of spasticity in pwMS measured at the end of IR. Furthermore, the randomization process should likely exclude a potential bias of anti-spasticity drug treatment on the performance of the "MS-spasticity APP" after IR.

In our pilot study we found no significant differences in the modified Ashworth scale between the two intervention groups. This finding could be attributable to the low sample size. However, a weak association of the patient-reported perception of spasticity and the Ashworth scale has also been reported previously in larger trials, probably reflecting the fact that the modified Ashworth scale measures resistance to passive movement only, but does not account for the range of features of spasticity that an individual patient experiences. In addition, the responsiveness to therapy of the 11-point NRS maybe superior to the 6-point modified Ashworth scale (Farrar et al., 2008).

A modern technology like an APP has the potential to enhance individual responsibility for regular exercising in pwMS. Whether the found effects can be generalized or whether they are the result of more versus less training can only be delineated in a subsequent study, that is powered to discriminate a therapeutic effect of this easily accessible and, once it has been established, overall inexpensive intervention. Nevertheless, what already can be derived from our pilot study are the caveats of the internet-wide use of an "MS-spasticity APP": professional medical advice, detailed personal instruction and repeated supervision can not be replaced by an APP, but are the essential prerequisites for its successful "application".

5. Contributors

RE, HFA and CB took part in study concept and design; collection, analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content and study supervision. KH, KD, YS and UM were

involved in design of exercises and collection of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. ME took part in analysis and interpretation of data; drafting of the manuscript and critical revision of the manuscript for important intellectual content.

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Conflicts of interest

All authors declare that there is no conflict of interest with any financial organization regarding the material discussed in this manuscript.

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