Treating MS-Fatigue with the Digital Therapeutic (DTx) elevida: Further Analyses from a Randomized Controlled Trial and First-Year Routine Care Experiences

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INTRODUCTION

Fatigue affects up to 70% of patients with multiple sclerosis (PwMS), is often experienced as the most disabling problem, and is linked with depression, cognitive impairment and early retirement.

Unfortunately, treatment options for MS-fatigue are limited and cognitive behavioral therapy (CBT), although promising, is rarely available to many patients due to a shortage of trained therapists or the fatigue itself.

CBT-based digital therapy programs (digital therapeutics) could improve the quality of treatment for MS-fatigue because they can be delivered flexibly and at low cost to large numbers of patients via the Internet.

We have developed the CBT-based digital therapeutic ‘elevida’, which has been shown to be effective in a randomized controlled trial with n=275 patients, in terms of reducing MS-fatigue over the course of 12 and up to 24 weeks.

OBJECTIVES

To describe the process by which elevida gained governmental approval for general reimbursement in Germany, and to report on the first year of experiences after this digital therapeutic has become widely available in the German healthcare system.

RELEVANCE

“To our knowledge, this trial is the largest of any published behavioral or pharmacological fatigue treatment trial in MS to date. [The trial showed that] the effects of elevida are comparable to those achieved by highly structured and supervised exercise interventions and behavioral interventions delivered in person, although self-guided programmes have much less requirements in terms of resources and infrastructure for delivery.” (Pöttgen et al., 2018)

METHOD

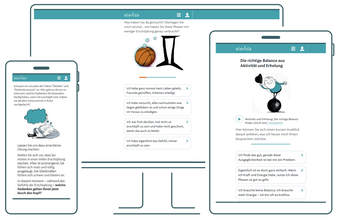
To gain approval for general reimbursement in Germany, further sensitivity analyses had been requested to confirm the robustness of trial results.

Therefore, we re-analyzed data from the elevida trial by using more conservative reference-based multiple imputation procedures.

The missing CFS values at 12 and 24 weeks were imputed, using the baseline CFS and sex as covariates in the imputation model. The imputation was conducted stratified by arm. A set of 100 imputations were performed.

Assumption	Description	Comment
Missing at Random (MAR)	Assume drop-out participants follow a similar behaviour to those from the same arm who stayed in the trial.	Primary analysis assumption (Pöttgen et al. 2018)
Jump to Reference (J2R)	Assume drop-out participants in the elevida group follow a behaviour similar to those in the control group.	Correspond to assuming „no treatment effect“ in those dropping out.

INTERVENTION: elevida

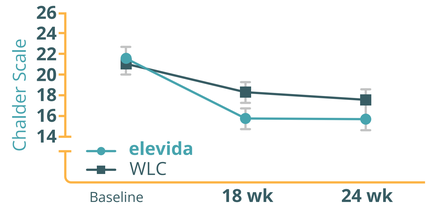


- Patients experience a simulated, dynamic dialogue between themselves and an empathetic expert.
- The dialogue format encourages active user involvement and facilitates users’ gradual skill acquisition, empowering them to combat fatigue with CBT techniques.
- elevida is fully automated, allowing HCPs to be as involved as they would like, but has been shown to also be effective in independent use as part of care-as-usual.
- As a web-based application, elevida offers the flexibility to fit with any existing treatment plan. Personal data and all information are treated with the highest standards of data protection and confidentiality.

RESULTS

The sensitivity analyses confirmed the presence of robust treatment effects (d = 0.30 - 0.39, ps < 0.02). Even under the assumption that drop-outs experienced substantially worse symptom courses than non-drop-outs, it could be confirmed that elevida led to significant and clinically relevant reductions in MS-fatigue over 12 and up to 24 weeks.

Results of the elevida RCT on fatigue reduction over 3 and 6 months (for further detail, see Pöttgen et al., 2018)



Results of the elevida RCT (Pöttgen et al., 2018) on effects of elevida on the Chalder Fatigue Scale. Symptoms of fatigue showed a stronger decline in the elevida group (n=139) compared with the waitlist control (WLC) group (n=136) and were maintained at long-term follow-up. Group differences were statistically significant at week 12 (p=0.0007) as well as week 24 (p=0.0080).

Even under conservative missing data assumptions, such as assuming that all drop-out participants experienced no treatment effect, the elevida effect on the primary outcome (CFS at 12 weeks) remained statistically significant, with a Cohen’s d of 0.39 (NNT = 3.4).

At 24 weeks, the difference was still in favor of elevida and remained statistically significant.

		elevida (N=139)	Control (N=136)	Difference between groups*		
Missing data assumption	Time-point	Mean CFS	Mean CFS	Mean [95% CI]	Cohen’s d [95% CI]	p-value
MAR	12 weeks	15.3	18.4	-3.3 [-4.9 to -1.7]	-0.50 [-0.75 to -0.26]	<0.001
	24 weeks	15.1	17.8	-2.8 [-4.4 to -1.2]	-0.43 [-0.67 to -0.18]	<0.001
J2R	12 weeks	16.1	18.4	-2.6 [-4.1 to -1.0]	-0.39 [-0.63 to -0.15]	0.001
	24 weeks	16.0	17.8	-2.0 [-3.6 to -0.4]	-0.30 [-0.55 to -0.06]	0.015

Pöttgen, J., Moss-Morris, R., Wendebourg, J. M., Feddersen, L., Lau, S., Köpke, S., Meyer, B., Friede, T., Penner, I., Heesen, C., & Gold, S. M. (2018). Randomised controlled trial of a self-guided online fatigue intervention in multiple sclerosis. Journal of Neurology, Neurosurgery & Psychiatry, 89(9), 970-976.

FIRST YEAR EXPERIENCES

Approximately one year after inclusion in the German directory of reimbursable digital therapeutics, elevida has been adopted by many treatment providers and MS clinics in Germany.

Prof. Dr. Gereon Nelles, Specialist in Neurology and Special Pain Therapy:
"It is encouraging to be able to provide MS patients with more than just pharmacological therapies."

Dr. Uwe Meier, Chairman of the Professional Association of German Neurologists:
"We neurologists don't have any therapies for fatigue, and I'm glad that I can now offer support to patients in this area. elevida is evidence-based, it has been proven in a study - that's reassuring. I've recommended elevida to well over 100 patients myself."

CONCLUSIONS

Based on these findings and after a thorough review by the German Federal Institute for Drugs and Medical Devices, elevida has become the first digital therapeutic for MS to be included permanently in the German government’s directory of reimbursable digital health applications, the "DiGA Verzeichnis".

Having recognized several important facilitators and barriers, we are confident that our efforts to disseminate elevida and integrate it in more routine care settings will continue to be successful.

elevida is currently available in English and German. Scan this QR code to learn more about elevida or contact us at **research@gaia-group.com**

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