Efficacy of a psychological online intervention for depression in people with epilepsy: A randomized controlled trial

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Summary

Objective: Depression is the most prevalent psychiatric disorder in persons with epilepsy (PWEs). Despite its major impact on quality of life and risk of suicide, most PWEs are not treated for depression. A current challenge in mental health care is how to close this treatment gap and increase access to psychological services. Psychological online interventions (POIs) have shown efficacy in improving depression among indi- viduals without neurologic disorders. This pilot study aimed to assess the feasibility and efficacy of a psychological online intervention for depression (Deprexis) in PWEs who have symptoms of depression.

Methods: Participants with self-reported epilepsy and subjective complaints of depres- sive symptoms were randomized to an intervention condition (Deprexis) or to a wait- ing list control (WLC) condition. After 9 weeks, participants were invited to complete an online reassessment.

Results: Relative to the waiting list group, program users experienced a significant symptom decline on the Beck Depression Inventory - I (BDI-I, primary outcome) with a moderate effect size in the complete observations analysis and a small effect size in the intention-to-treat analysis. Furthermore, there was a significant improvement with a moderate effect size on the “energy/fatigue” subscale of the Quality of Life In Epilepsy Inventory - 31 (QOLIE-31).

Significance: The results of this trial suggest that POIs may be a feasible and beneficial tool for PWEs who have comorbid depressive symptoms.

KEY WORDS: Depression, Epilepsy, Internet intervention, iCBT, Deprexis. Depressive disorders are the most frequent comorbid psychological conditions in persons with epilepsy (PWEs), with lifetime prevalence rates of 30–35%.[1]

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Depressive disorders are the most frequent comorbid psychological conditions in persons with epilepsy (PWEs), with lifetime prevalence rates of 30–35%.[1] Patients with uncontrolled seizures are diagnosed with major depression twice as often as patients with controlled seizures.[2] Depressive symptoms, as well as seizure worry, have a major impact on the quality of life of affected indi- viduals,[3] irrespective of the type of recent epileptic seizures.[4]

A recent systematic review suggests that psychological interventions, such as cognitive behavioral therapy (CBT), are effective if they are particularly focused on the reduction of depressive symptoms rather than on the reduction of sei- zure frequency.[5] Given physician-related treatment barriers related to fears of lowering seizure threshold and adverse drug interactions between antidepressants and antiepileptic drugs (such as, reciprocal inhibitory or excitatory effects on drug metabolisms), [6] as well as reluctance among PWEs to engage in therapy because of fear of stigmatization,[7] alter- native methods of delivering treatment are needed. In the past decade, technological advances in Internet-based com- munication have created the potential to make psychologi- cal services more convenient and accessible to consumers.[8] PWEs are often interested in exploring novel approaches, but unfortunately, research on the applicability and efficacy of such approaches for depression in PWEs is rare,[9] in con- trast to the well-grounded evidence on psychological online interventions (POIs) for depression in general. A meta-analysis that included seven randomized controlled trials (RCTs) of self-guided psychological interventions for depression (one self-help book and six Internet-based self- help programs based on CBT methods [iCBT]) confirmed their efficacy, demonstrating an average small effect (d = 0.28).[10] A subsequent meta-analysis that included 19 studies on computer- and Internet-based interventions for depression (based on several psychological treatment approaches) supported these findings and reported a moder- ate posttreatment pooled effect size (d = 0.56).[11] POIs for depression hold promise, both as self-help applications and as adjunctive therapies to usual care.[12]

Trial objective

This pilot study aimed to evaluate the feasibility and effi- cacy of a POI program for depression (Deprexis; see Inter- vention section) in individuals with epilepsy and comorbid depressive symptoms. The primary outcome of the study was depressive symptoms as assessed with the Beck Depression Inventory I (BDI-I; see the Questionnaires sec- tion). A secondary aim was to assess whether quality of life is improved by the intervention.

Methods

Recruitment

Between May 2012 and July 2013, a patient database from the Epilepsy Center Alsterdorf was used to invite patients via mail. Further patients were invited via postings in moderated epilepsy-specific online forums (http:// forum.epilepsie-netz.de/ and http://www.epilepsie-onli- ne.de/forum/). Individuals without self-reported epilepsy diagnoses or depressive symptoms were excluded automati- cally from the online survey and were blocked from re-par- ticipation by means of "cookies." Beyond that, self-reported epilepsy diagnoses were externally validated based on an epilepsy-specific inventory, the Performance, Sociodemo- graphic Aspects, Subjective Estimation (PESOS) question- naire (see Questionnaires section), by conducting plausibility checks for each participant. The study invitation summarized the basic study design, and it was made clear that all participants would receive free-of-charge access to the online program (either immediately or at the end of the study), which would automatically expire after the intervention period of 9 weeks. No financial reimbursement was offered for study participation.

Baseline assessment

A Web-link in the postal and forum invitations directed potential participants to the baseline survey, which was implemented using the software package EFS Survey (www.unipark.info). The online survey program prevented multiple logins from the same computer to the baseline sur- vey by the use of "cookies." We obtained an online informed consent for each participant in accordance with regulations by the Ethics Committee of the Medical Associ- ation, Hamburg. The baseline survey proceeded with sec- tions as follows: inquiry of sociodemographic information, clinical history (e.g., current treatments, psychiatric diagno- ses), a psychopathologic (e.g., depression), and a psycho- logical section (e.g., quality of life). The psychological and psychopathologic sections encompassed several question- naires that are described in detail in subsequent text. At the end of the survey, participants were required to enter their e-mail addresses. Completing the baseline survey required approximately 40 min.

Inclusion and exclusion criteria

Inclusion criteria were liberal because we aimed to acquire a clinically representative sample to maximize external validity and, thus, relevance for clinical practice.[13] For example, although age and currently being in psycho- therapy or using pharmacologic treatment did not lead to exclusion, these variables were examined for their effect on outcomes. It was not our aim to verify a clinical diagnosis of depression, because we conducted our trial using low- threshold criteria including subclinical depressive symp- toms. The reason for low-threshold studies was to reach people that usually fall through the cracks of health care because of subclinical depressive symptoms or reluctance to undergo face-to-face treatments or diagnostic assess- ments.

Individuals without self-reported epilepsy diagnoses, without self-reported depressive symptoms, and with acute suicidal ideation, and those lacking sufficient time to take part

in the online program for 9 weeks, were excluded from participation. Reporting diagnoses of psychosis or bipolar disorder, as well as suicidality, led to immediate exclusion by means of a “trap door” in the survey program, which ter- minated the assessment by informing participants about the respective reasons for their exclusion. For subjects with sui- cidal tendencies, telephone numbers of institutions special- ized in the treatment of suicidality were displayed.

Treatment allocation

Included participants who provided their e-mail addresses at the end of the baseline survey were randomly allocated to the treatment or WLC group. Allocation was done in consecutive order using a computer-generated ran-

dom number table. No stratification was applied. Partici- pants in the immediate treatment group received detailed instructions via e-mail on how to log into the Deprexis sys- tem using an access code that allowed full use of the pro- gram for the duration of 9 weeks, starting at the time of registration. Those in the WLC condition (delayed treat- ment) received notice via e-mail that they were allocated to the control group and would receive their access code upon completion of the follow-up assessment 6 months later.

Intervention

This trial used the Internet-based program Deprexis,[14] which is aimed at reducing symptoms of depression. It com- prised predominantly elements of CBT, such as cognitive restructuring and behavioral activation, and complements these with mindfulness and acceptance exercises, among others. Users interact with the program via a simulated dia- logue, in which they are continuously asked to select one of several response options and are presented with subsequent content that aims to match their expressed preferences and requirements. Depending on reading speed and each user’s individual path through the program, each module lasts approximately 10–60 min.

Reassessment (after 9 weeks)

Nine weeks after the baseline assessment, participants were sent an e-mail invitation to take part in the second evaluation that included a link directing them to the posttreatment survey. To achieve a high completion rate, up to three reminders were sent via e-mail if the partici- pants did not respond to the invitation e-mail. At the beginning of the posttreatment survey, participants were requested to enter the same e-mail address as in the baseline survey for identification and matching of pre- and postdata. The post assessment contained the same questionnaires as the baseline survey (see Questionnaires section). In addition, participants in the treatment condi- tion were asked questions relating to subjective appraisal of the program.

Sample size

Sample size calculation, performed using G*Power,[15] revealed that 80 patients (full sample) would be neces- sary to detect a significant difference when assuming a medium–large effect size of treatment over the control condition at an a-level of 0.05 and a power of 0.95 (two-tailed; considering 25% dropout). Recruitment stopped after 81 patients had completed the baseline survey. Three of those 81 were excluded prior to the baseline analyses, so that 78 participants remained in the sample. One of those three was lost due to technical issues with the survey program, and two others were excluded because they stated they had given untrue answers to some of the questions in the survey.

Questionnaires

The Beck Depression Inventory (BDI-I),[16] which served as the primary outcome of the study, is a self-report ques- tionnaire containing 21 items. It represents a common instrument for the assessment of depression severity. Inter- nal consistency for both psychiatric and nonpsychiatric pop- ulations is above 0.8.[16] The BDI was subdivided into three subscales: negative attitude toward self, performance impairment, and somatic symptoms.[17]

The PESOS questionnaire for PWEs assesses individual impairment due to epilepsy.[18] In addition to objective parameters, such as demographic data, seizure frequency, and further clinical aspects, subjective questions are posed that are focused on illness-specific difficulties and limita- tions, such as disability in everyday life, mobility and inde- pendent life, social relationships, physical and mental conditions, epilepsy-specific anxiety, stigma-related prob- lems, emotional adaptation, job-related difficulties, parent-related difficulties, and school-related difficulties. The internal consistency of the PESOS subscales is adequate (Cronbach's a = 0.75–0.89), as well as the criterion-related validity with the Quality of Life in Epilepsy Inventory (QOLIE-31, see below) of r = 0.71. The questionnaire originally contains 58 items, but for the online survey of this trial, only those items that were deemed necessary to vali- date a diagnosis of epilepsy were used.[18]

The World Health Organization (WHO) Quality of Life questionnaire (WHOQOL-BREF) is an abbreviated 26-item version of the WHOQOL-100 that was developed by the WHOQOL Group in 1995 to measure quality of life in persons with physical or psychological illnesses, as well as in those without any health impairments. The measure cov- ers four domains: physical, psychological, social, and envi- ronmental quality of life.[19]

The Quality of Life in Epilepsy Inventory (QOLIE-31)[20] contains seven subscales that tap emotional well-being, social functioning, energy/fatigue, cognitive functioning, seizure worry, medication effects, and overall quality of life. The QOLIE-31 overall score is obtained by a weighted aver- age of the different dimensions that include 30 items in total.

For participants who were assigned to the intervention group, additional questions relating to the subjectively per- ceived efficacy and feasibility of the program were posed. Further, several questions probed the intervention's applica- bility to the specific issue of depressive symptoms in PWEs.

Strategy of data analysis

All statistical analyses were conducted blinded and by using IBM® SPSS® Statistics 22.0 (Armonk, NY, U.S.A.) software. Complete observations analyses were conducted for participants using a linear mixed model (LMM) approach in view of statistical studies suggesting that an LMM yields higher power to detect group differences and can utilize all available data.[21] All results are reported using restricted maximum likelihood (REML) estimation and the Satterthwaite approximation to calculate the denominator degrees of freedom. Following the advice of Barr et al.[22] in terms of the random effects structure, for each result, the individual participant is utilized as a random intercept, and time between assessments in weeks is used as a random slope. The parameter estimate of interest for each model is the interaction term group (Deprexis vs. WLC) 9 time (baseline vs. post), which contains the information if a sig- nificant change between the two groups exists over time. Effect sizes are reported as Cohen's d ($d \leq 0.2$ % small effect, $d \leq 0.5$ % moderate effect, $0.8 \leq d$ % large effect).

Results

Baseline differences

Sociodemographic and clinical baseline characteristics of each group are presented in Table 1. Randomization was generally successful because no significant differences between the intervention group and the control group emerged for most variables, except for age: $F(1, 76) = 2.01$, $p = 0.048$. Participants in the WLC group were, on average, 5 years older (40 years; range 22–70) than participants in the intervention group (35 years; range 18–57). To take this group difference into account, the variable "age" was entered as a covari- ate in the statistical analyses.

Approximately 75% of all subjects were female, 47% had at least high school education (13th grade), and 25% received some kind of psychotropic medication. With focus on antiepileptic medication, almost half of the anticonvulsive drugs were well-tolerated in both groups. Again, there was no difference between the WLC and the intervention group in terms of seizure type and frequency. On average, both groups had predomi- nantly minimal–mild depressive symptoms (BDI score ≤ 18) with an average BDI score of 19 (range 2–40) in the WLC and 22 (range 5–49) in the intervention group

(see Table 2). Almost half of the participants (47.4%) reported receiving some kind of depression treatment at baseline.

Group comparisons

Completion

The overall completion rate for the main outcome at post assessment was 72%, with no statistically significant differ- ence between the intervention group (63%) and the control group (80%): $v^2(1) = 2.00$, $p = 0.157$. Three participants were missing because one subject withdrew consent during the course of the trial, and in two cases there was a delivery failure of the invitations to the via email postassessment. Another subject cancelled halfway through the online survey, so corresponding data are available for the BDI but not for the rest of the measures.

Statistical analyses

Analyses on complete observations were conducted for the primary and secondary outcomes. The main effect of the covariate, age, did not yield significance in any of the analy- ses. Results are summarized in Table 2, indicating that patients in the intervention group showed a significantly greater symptom reduction on the BDI-I total score than subjects in the WLC, with a moderate effect size $F(1, 55.96) = 7.14$; $p = 0.01$; $d = 0.46$. The extent of this effect size corresponded with a substantial improvement of 6.24 BDI points, on average, for the intervention group. However, the WLC group also improved slightly (1.41 BDI points) across time (see Table 2).

In addition to the analyses utilizing all available data, intention-to-treat (ITT) analyses were performed for the pri- mary outcome (BDI-I) and for all secondary outcomes with the last observation carried forward (LOCF) method, that is, the baseline observation. Results, displayed in the final col- umn of Table 2, did not change except for the BDI subscale “negative attitude toward self,” which was not significant anymore.

Table 1. Sociodemographic and clinical background information of WLC and intervention group at baseline

There was no significant difference in the quality-of-life gain between the intervention group and the WLC over time as measured using the four domains of the WHOQOL-BREF. There was also no significant group difference over time in the epilepsy-specific quality of life measure, the QOLIE-31, $F(1, 76) = 0.098$; $p = 0.755$; $d = 0.04$, but in the subscale “energy/fatigue” we found a significant differ- ence between intervention group and WLC with a moderate effect size, $F(1, 76) = 4.274$; $p = 0.042$; $d = 0.32$, as well as a statistical trend for the subscale “social function,” $F (1, 76) = 2.812$; $p = 0.098$; $d = 0.21$ (Table 3).

Subjective appraisal

Table 4 provides data on the retrospective appraisal of the program from participants who were randomized into the intervention group and had logged into the program at least

once. Most of the participants were satisfied with the program, would use it again, and appraised it as suitable for depressive symptoms that accompany epilepsy. Although participants see the program as a suitable adjunct to their medical treatment and a tool to bridge waiting time for psy- chotherapy, only a minority found the program appropriate as a substitute for psychotherapy. A slight majority reported that the program should be better adapted to the special needs of PWEs. Most suggestions in this respect referred to the wish of including more epilepsy-related topics: how to deal with stresses and strains that go along with seizures, how to react to the stigmatization of PWEs and psycho-edu- cation regarding the relationship of epilepsy and depression.

Discussion

The study investigated the efficacy and feasibility of a psychological online intervention for depression (Deprexis) in PWEs and comorbid depressive symptoms. The comple- tion rate (73%) was a little lower than in equivalent trials with samples of individuals with depression (81.9%)[23] or individuals with depression associated with multiple sclero- sis (79%).[24]

The majority of PWEs appraised the intervention pro- gram as “good” and “helpful to treat depressive symptoms” (see Table 2). Subjective appraisal was confirmed in the complete analyses for the BDI-I, where significant improve- ments with small to moderate effect sizes emerged for the total score, as well as the subscales “negative attitude towards self” and “performance impairment.” The signifi- cant results for the BDI total score were reproduced in an ITT (LOCF) analysis with small effect sizes. The effect was not due to concomitant treatment; groups did not differ in treatment (or treatment changes) with antiepileptic drugs during the intervention period. We consider this symptom reduction to be a meaningful change, which implies that a larger trial on PWEs with comorbid depressive symptoms using Deprexis or other online treatment programs should be conducted in the future (including analyses on the mechanisms of efficacy, and the impact of adherence and attitudes toward psychotherapy on efficacy, as well as effectiveness trials in natural settings).

Table 2. Group comparisons on the primary outcome measure (BDI) for baseline, end point, and across time

Table 3. Group comparisons on the secondary outcome measure QOLIE-31 for baseline, end point, and across time

On the measures tapping epilepsy-specific quality of life (QOLIE-31) and quality of life in general (WHOQOL- BREF), significant improvement emerged on only one sub- scale of the QOLIE-31 (“energy/fatigue”). This result might be due to the behavioral activation, as well as the physical exercise and lifestyle modification modules of

Deprexis. This improvement is in line with the symptom reduction in the BDI "performance impairment" item "fatigue."[17] We speculate that no improvements on other subscales of the QOLIE-31 emerged due to a lack of epilepsy-related themes covered by Deprexis.

In their subjective appraisal of Deprexis, most partici- pants found that the program should be adapted to the spe- cial needs of PWEs with respect to involving more epilepsy-related topics. "Tailoring"[25] Deprexis to PWEs, could increase the acceptability as well as the effectiveness of the intervention in this particular patient group.

Some limitations of this pilot study need to be addressed before turning to the conclusions. First, the recruitment pro- cess was very slow, indicating that PWEs had no great inter- est in either online trials or the intervention. Still, subjective appraisal of the intervention was good, which speaks for the need for different recruitment strategies in further trials.

Second, diagnosis of both epilepsy and depressive symp- toms relied on self-report measures instead of direct contact. Self-assessments conducted online have been shown to be valid[26] and are therefore used with increasing frequency. A recent meta-analysis concluded that self-reports yield more conservative estimates of treatment efficacy than clinician ratings.[27]

A further problem concerns a possible recruitment bias. Because of the self-selectivity nature of online studies, it could be that participants were exceedingly motivated or suitable for psychological online interventions. Such inter- ventions might be particularly attractive for people who are well-versed in using the Internet, or those with a preference for alternative treatment approaches, a reluctance to seek direct treatment, or dissatisfaction with conventional inter- ventions.[27] To avoid this bias, more trials in natural settings are warranted, in light of the promising results of the pri- mary effectiveness trials.[28]

Further problems that often accompany online trials and interventions are high dropout rates and difficulty assessing the reasons for attrition. Regarding the present trial, there was an absolute, but not statistically signifi- cant difference in dropout rates between groups, such that fewer participants dropped out in the control group. Therefore, assumptions for the LOCF method (missing values are missing completely at random) were not vio- lated. This was also supported by conducting all analyses using a per-protocol method (not presented here) that did not alter any of the results. Nevertheless, one should bear in mind that future research should address any potential dropout bias rigorously, either by implementing an active control or by other means. Although, we tried to prevent dropouts in this study by sending e-mail reminders, it must be noted that completion rates were slightly worse than in an equivalent study by our research group in par- ticipants with depression without neurologic disorders,[23] as well as in depressed

participants with depression and 24 other neurologic disorders.

The present article reports an interim analysis. Accord- ingly, we are well aware of the rising probability of a type-1 error for the upcoming analysis of follow-up data. In light of this, the present results have to be considered preliminary and should be investigated further when all data are avail- able using appropriate methods to control for the higher type-1 error rate. Secondly, because this trial is of a preli- minary nature, in the future our results need to be replicated in individuals with confirmed diagnoses of epilepsy and control groups of PWEs without depressive symptoms, PWEs with depression, and depressed patients without epi- lepsy.

To conclude, the present study contributes to a growing empirical basis highlighting the benefits of POI for depression. Interventions such as Deprexis may help to close the existing treatment gap due to their accessibility and efficacy.[14,23,29] It is also important to note that most Internet interventions that claim to reduce depressive symptoms have no evidence base at all and should be tested in independent randomized controlled trials before they can be regarded as safe and efficacious. Effective POI programs for people with symptoms of depression can potentially have a large impact at a population health level—even with 30 symptoms. Face-to-face therapy should still be recom- mended as the standard for depression treatment, but POIs can be regarded either as feasible alternatives or as a possi- ble adjunct to traditional treatment approaches.

Acknowledgments

All authors were substantially involved in the study or preparation of the manuscript. The Trial is registered at: clinicaltrials.gov (NCT01663649) and received approval from both the local ethics committee and the depart- ment of data security in Hamburg (Germany).

Disclosure or Conflicts of Interest

There was no conflict of interest for any of the authors. GAIA AG, the developer and distributor of Deprexis, neither interfered with the study design nor provided direct support (e.g., subject recruitment). In case of technical questions, patients were able to turn to technical support (info@deprexis.de), but the staff did not inquire or comment on the study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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