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Feasibility, effectiveness and safety of the self-management intervention deprexis in routine medical care: Results of an uncontrolled observational study

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ABSTRACT

Introduction: Numerous RCTs have demonstrated the effectiveness of internet-based self-management interventions (SMIs) in the treatment of depressive symptoms. These studies often recruit outside routine clinical practice. For the present study, we investigated the feasibility, effectiveness and safety of an SMI (deprexis) in routine medical care using a non-interventional design.

Methods: A total of 104 patients with a depressive disorder (60.58% female, mean age 45.82 yrs) were recruited in 25 outpatient practices in Germany (mostly psychiatric practices, $n = 16$). They received 12 week access to the SMI in addition to their usual care (76.0% took concomitant antidepressant medication). Guidance could optionally be offered by the treating physician. The effectiveness of the intervention was assessed using the clinician-rated short version of the Montgomery Asberg-Depression Scale (svMADRS) and the Patient Health Questionnaire (PHQ-9), a self-rating for depressive symptoms. Outcomes were assessed at baseline as well as at weeks 3, 6, 9 and 12.

Results: Most patients reported using the intervention at least once ($n = 87$, 83.6%), among these users the mean number of sessions was 18.05 (SD = 11.33). Only a minority of patients received the guided version of the intervention ($n = 7$, 8.0%). The severity of depressive symptoms decreased significantly over the observation period from 29.72 (SD = 10.03) to 15.73 (SD = 9.74) for the svMADRS (Cohen's d = 1.42, 95% CI 0.08–2.76) and from 15.20 (SD = 5.03) to 8.77 (SD = 5.03) for the PHQ-9 (d = 1.29, 95% CI 0.60–1.97).

Discussion: The size of the pre-post effect on depressive symptoms observed in this study is comparable to the pre-post effect size reported in an RCT using the same intervention in patients suffering from depressive symptoms of the same severity. Limitations of this study include the lack of a control group and the fact that the recruitment rate was far lower than expected.

Conclusion: This non-interventional study conducted in outpatient practices confirms results from numerous RCTs. Taken together, these data show that deprexis can be used effectively and safely in the routine care of depressed outpatients.

1. Introduction

Depression is very common but often remains untreated (Jacobi et al., 2014; Nübel et al., 2019). Reasons for this treatment gap include structural factors, including long waiting lists. More often, though, patients with depression or other severe mental disorders name the desire to solve their problems on their own as a reason for not seeking treatment (Kessler et al., 2001; Nübel et al., 2019). Internet interventions might therefore be an opportunity to reduce the treatment gap (Schröder et al., 2016). One group of internet interventions are self-management interventions (SMI) which are mostly based on theories and techniques of cognitive behavioural therapy (CBT). SMIs have been shown to be effective in the treatment of depression (Karyotaki et al., 2017), resulting in clinically relevant changes (Karyotaki et al., 2018a) with no evidence of an increased risk of harmful effects (Karyotaki et al., 2018b).

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One SMI that has been studied in numerous trials, is deprexis®24 (hereafter "deprexis", for a meta-analysis, see Twomey et al., 2020). In these trials, this SMI has demonstrated its effectiveness not only in mild to moderate depression (Klein et al., 2016) but also in severe depression (Meyer et al., 2015). The intervention has also been used successfully in patients who suffer from depressive symptoms in the context of multiple sclerosis (Fischer et al., 2015), epilepsy (Schröder et al., 2014) and in problem gamblers (Bücker et al., 2018). The participants in most of these studies were self-selected and recruited outside routine clinical practice. Two published RCTs of deprexis have examined the effectiveness of blended therapy in routine clinical settings. Here, deprexis was added to in- and outpatient psychotherapy respectively (Berger et al., 2018; Zwerenz et al., 2019, 2017).

Other SMIs have also been tested in routine clinical settings. Randomized clinical trials of these interventions have yielded mixed results: one study conducted in primary care in Britain found that the addition of *MoodGYM* or *Beating the Blues* to usual primary care did not convey an added benefit, possibly because the interventions were used only once (*MoodGYM*) or twice (*Beating the Blues*) by most patients (Gilbody et al., 2015). These results shed some doubt on the feasibility of using SMIs in routine clinical care and suggest the need of further studies. Another German study, also conducted in primary care, found that *MoodGYM* was more effective than usual care in reducing depressive symptoms; but again only 70% of patients used the intervention (Löbner et al., 2018). Moreover, in a large uncontrolled study conducted in primary care in Australia, it was found that the treatment program *Sadness* worked with large pre-post effect sizes on symptoms of depression (Williams and Andrews, 2013). Most of the available studies focussed on the effectiveness of SMIs and only a minority of studies systematically assess adverse events (Karyotaki et al., 2018b; Moritz et al., 2019).

For the present study, we have therefore investigated the feasibility, effectiveness and safety of the SMI deprexis using an observational design. We have put particular emphasis on assessing adverse events. In the spirit of an effectiveness trial, we have recruited only patients who started deprexis as part of their routine medical care (Leichsenring, 2004).

2. Methods

2.1. Study procedures

This is a single-group, uncontrolled, prospective observational study of adult patients with a depressive disorder (either dysthymia or depressive episode) who were starting treatment with deprexis as part of their routine medical care. Patients were recruited in Germany through the following outpatient services: general practicioners ($n = 4$), neurologists ($n = 5$) and psychiatrists ($n = 16$) between October 2016 and February 2018. To enhance external validity, all patients could be included into this study regardless of presence or absence of comorbid disorders or concurrent medication. The trial was approved by an Ethics Committee Freiburg (016/1259) and is registered with German Trials Register (DRKS00011628). Written informed consent was obtained prior to the baseline assessment. The full study protocol has been laid down in writing before the initiation of patient recruitment and is available upon request. The following change has been made to the protocol after the initiation of the trial: the initial goal was to recruit up to 1800 patients to the trial, but recruitment was stopped after including only 104 patients because recruitment was much slower than anticipated and the duration of recruitment had already been extended from 9 months to 17 months.

2.2. Intervention

All participants received access to the deprexis for 12 weeks in addition to their usual care (for more information on the actual care received, please see the Results section). Access to deprexis was provided at a reduced cost of 179 € (instead of 297.50 €) because deprexis was not part of regular care in the German health care system when the study was conducted (some insurance companies did cover the cost, however). The content of deprexis is broadly consistent with the principles of CBT. It is divided into six to ten modules ranging from behavioural activation and cognitive modification to dreamwork and is individually tailored to the user. The number and order of modules as well as its depth and breadth can vary depending on the user's preferences (for example, the "interpersonal skills" module is offered to some patients while the "behavioural activation" module is offered to all patients). It is recommended that users complete one to two sessions of about 30 min per week (for more details, see Meyer et al., 2009 and Twomey et al., 2017). The intervention can be used with or without guidance by a clinician (Berger et al., 2011). For the guided version, messages can be sent through a secure email-system embedded within the internet intervention. In our trial, the guided version could be offered by the treating physician (but it was not routinely offered). Frequency and content of guidance were not influenced by the study team.

2.3. Outcome measures

The usage of the intervention was measured using patient self-report. Note that the number of sessions does not necessarily reflect the number of completed modules because it can take more than one session to complete a module. The effectiveness of the intervention was assessed using the clinician-rated short version of the Montgomery Asberg-Depression Scale (svMADRS: Montgomery and Asberg, 1979) and the Patient Health Questionnaire (PHQ-9: Kroenke et al., 2010), a self-rating for depressive symptoms. Higher scores on the svMADRS and the PHQ-9 reflect higher severity of depressive symptoms. Clinicians also completed the Clinical Global Impression (CGI) score and patients also completed the Sheehan Disability Scale (SDS: Sheehan and Sheehan, 2008) and the Client Satisfaction Questionnaire (CSQ-4: Attkisson and Greenfield, 2004). For the SDS, higher scores reflect more severe disability in work, social and family life; for the CSQ-4, higher scores are associated with greater satisfaction. Patients also completed two items from the Compulsive Internet Use Scale (CIUS: Besser et al., 2017). The time reference for these scales was the past two weeks (expect for the svMADRS and the lost days subscale of the SDS, here it was one week). All outcomes were determined at baseline as well as at weeks 3, 6, 9 and 12. At these assessment time points, physicians also assessed the patients' medication status and completed standardized adverse events forms to document safety-relevant incidents and adverse events.

2.4. Statistical analysis

Statistical analysis was performed by a contract research organization (ANFOMED GmbH, Germany) using SAS™ following a previously agreed upon statistical analysis plan (SAP). Missing values were replaced using last observation carried forward if at least two entries were made for this variable, i.e. the baseline value and at least one value after baseline (modified intention to treat analysis). This was used as a conservative estimate of actual symptom course because many patients show improvement even in untreated depression (Cuijpers et al., 2020). All statistical tests should be interpreted in a descriptive-explorative way and are reported as two-tailed tests with an p-value of < 0.05 used to assess statistical significance. Wilcoxon's signed-rank tests were calculated for continuous variables and Bhapkar's Test of marginal homogeneity was used for nominal variables.

3. Results

3.1. General characteristics

A total of 104 patients with a depressive disorder were recruited in 24 centres (mean patients/centre = 3.46, *SD* = 4.91). Retention rate was 92.3% (*n* = 96), 86.5% (*n* = 90) and 84.6% (*n* = 88) at the assessment weeks 3, 6, 9 and 12 respectively. Participants were predominantly female (60.58%, *n* = 63), they had a mean age 45.82 yrs. (*SD* = 12.2) and only 29.81% (*n* = 31) had completed highest secondary education (37.68%, *n* = 39 were employed full-time). A total of 30 patients (28.8%) reported using private use of the internet for more than 2 h per day.

3.2. Clinical characteristics

A total of 44 patients (42.3%) met criteria for a first depressive episode, 49 patients (47.1%) had a recurrent depressive disorder and 8 (7.7%) patients were diagnosed with dysthymia. The mean number of previous depressive episodes was 4.54 (*SD* = 4.76), the mean duration of the current depressive episode was 18.05 weeks (*SD* = 31.16). Regarding further indices of chronicity, the treating physicians reported that 47.5% of patients (*n* = 48) had not experienced remission for more than two years and that 70.6% (*n* = 72) had first experienced depression before the age of 21.

A past history of suicide attempt was reported by 11 patients (10.7%). According to the treating physician, a total of 46 patients (44.2%) had comorbid psychiatric disorders, mostly anxiety disorders (26%, *n* = 27) and substance dependence (9.6%, *n* = 10); and a total of 46 patients (44.2%) had comorbid somatic disorders (e.g. metabolic disorder, gastrointestinal disorder or cardiovascular disorder). With respect to treatment history, 70,9% (*n* = 73) had previously been treated with an antidepressant (38.5% used an SSRI, *n* = 40; 26.4% were treatment-resistant, *n* = 23) and 33.7% (*n* = 35) had received psychotherapy in the past months (mostly cognitive behaviour therapy, *n* = 17, and psychodynamic therapy, *n* = 13). At baseline, 76.0% were taking antidepressant medication (*n* = 79; *n* = 40, 38.5% were on an SSRI) and 33.6% were in psychotherapy (*n* = 35).

3.3. Intervention usage

Most patients reported using the intervention at least once (*n* = 87, 83.6%), among these users the mean number of sessions was 18.05 (SD = 11.33). A total of 20.2% (*n* = 21) were coded as terminating the use of the intervention prematurely; but this number includes loss-to-follow-up (*n* = 7) as well as lack of compliance (*n* = 5) and inadequate internet access (*n* = 3). Most patients reported spending between 30 and 60 min per session (*n* = 51, 63.0% at week three, *n* = 47, 58.1% at week six, and *n* = 50, 63.3% at week twelve). Only a minority of patients received the guided version of the intervention (*n* = 7, 8.0%).

3.4. Clinical outcome

All clinical outcomes for all assessment time points are presented in Table 1. Briefly, the severity of depressive symptoms decreased significantly over the observation period from 29.72 (*SD* = 10.03) at baseline to 15.73 (*SD* = 9.74) at week 12 for the clinician-rated svMADRS ($p < .0001$, Cohen's $d = 1.42$, 95% CI 0.08–2.76) and from 15.20 (*SD* = 5.03) to 8.77 (*SD* = 5.03) for the patient-rated PHQ-9 ($p < .0001$, $d = 1.29$, 95% CI 0.60–1.97). With regard to functional impairment in social life, the total score on the SDS significantly decreased from 19.90 (*SD* = 6.54) at baseline to 11.36 (*SD* = 6.34) at week 12 ($p < .0001$, $d = 1.33$, 95% CI 0.38–2.28). Also, the clinician-rated severity of illness as assessed by the CGI decreased significantly from 69 patients (67.0%) being rated as markedly ill or worse at baseline to only 9 patients (10.2%) at week 12 ($p < .0001$, *RR* = 0.15, 95% CI 0.08–0.29); 28.9% (*n* = 28) were rated as "very much improved" and 42,3% (*n* = 41) as "much improved" at week 12.

3.5. Patient satisfaction

On the CSQ-4, the sum score at week 12 was 12.36 (*SD* = 2.12) out of a total of 16 points. More specifically, 55 patients (68.75%) reported that "most (or all) of my needs have been met", 75 answered that the intervention "helped (a great deal)" (93.75%) and 69 patients said they would (definitely) use the intervention again (86.25%).

3.6. Adverse events

Two adverse incidents (feeling of paralysis and increase in depressive symptoms) and one serious adverse event (acute suicidality) were reported by the treating physicians. Only the feeling of paralysis was considered to be causally related to deprexis by the treating physician. The patient reporting an increase in depressive symptoms felt overwhelmed by deprexis. Consequently, treatment with the intervention and participation in the study were terminated. The other two patients were followed up and were reported as recovering (suicidality) and recovered (paralysis spontaneously recovered after a few hours).

3.7. Internet usage

Self-reported total internet usage did not change substantially during the study period: the number of patients who reported private use of the internet for 2 h or more per day increased slightly from 30 (28.8%) at baseline to 33 (35.5%) at week three and decreased thereafter to 23 (25.8%) at week six and 18 (21.2%) at week twelve. Likewise the number of patients who reported that they often or very often continued using the internet even though they actually wanted to quit decreased from 23 (22.1%) at baseline, to 19 (20.7%) at week three, 9 (10.0%) at week six and 6 (7.1%) at week twelve. The same was true for the number of patients reporting that they often or very often neglected obligations because of spending time on the internet, this decreased from 9 (8.6%) at baseline, to 8 (8.7%) at week three, 4 (4.4%) at week six and 4 (4.7%) at week twelve.

4. Discussion

This observational study in depressed patients treated in routine care remained far below the recruitment target. It found that the usage intensity of deprexis was adequate and associated with improvement in range of outcomes: a decrease in both clinician- and self-rated depressive symptoms, a decrease in disability and an increase in global functioning. Only a small minority of patients experienced adverse events. We also found a decrease of uncontrolled internet use over time suggesting that treatment with deprexis was not associated with the emergence of symptoms of internet use disorder. This is a reassuring finding given that symptoms of depression are strongly associated with problematic internet use (Carli et al., 2013).

One central limitation of this study is that actual recruitment fell far short of the recruitment target. This is probably due to the fact that in contrast to other clinical studies, some participants in this study had to pay for the use of deprexis (albeit at a somewhat reduced price) because in Germany, SMIs were not covered by the statuatory health insurance then. This has changed in 2020, however, with the advent of the Digital Care Act (Digitales Versorgungsgesetz) which provides that certain internet interventions can be listed and reimbursed by the statuatory health insurance (Geirhos et al., 2019). Other RCTs that aimed to recruit in routine clinical settings had similar problems, even if the SMI was offered at no cost to patients (Berger et al., 2018; Klein et al., 2017). This suggests that clinicians and patients do not yet routinely consider SMIs as an option along with the more traditional treatment options (i.e. psychotherapy and psychopharmacotherapy). This may

Table 1
Clinical outcomes.

	Baseline		Week 3		Week 6		Week 12	
PHQ-9 (n = 95)	15.20	5.03	12.95	4.82	10.53	4.55	8.77	5.03
svMADRS (n = 82)	29.72	10.03	26.46	9.85	20.66	8.99	15.73	9.74
SDS (n = 87)								
Total score	19.90	6.54	18.07	5.89	14.67	5.99	11.36	6.34
Occupational	6.67	2.53	6.06	2.35	5.11	2.47	3.91	2.33
Social life	6.74	2.51	6.23	2.22	5.00	2.19	3.87	2.35
Family/home	6.49	2.39	5.76	2.16	4.55	2.06	3.57	2.21
Lost days	4.09	2.86	3.81	2.68	3.35	2.44	2.40	2.11
CGI-S (n = 85)								
Normal					2	2.3%	3	3.4%
Borderline ill			1	1.1%	3	3.4%	10	11.4%
Mildly ill	8	7.8%	9	9.6%	16	18.0%	35	40.0%
Moderately ill	26	25.2%	32	34.0%	52	58.4%	31	35.2%
Markedly ill	46	44.7%	43	45.7%	14	15.7%	9	10.2%
Severely ill	19	18.5%	9	9.57%	2	2.5%		
Extremely ill	4	3.9%						
CSQ-4 (n = 81)	n.a.						12.36	2.12

Clinical outcomes are reported as means (standard deviations) and numbers (%) respectively. Missing values were replaced using last observation carried forward if at least two entries were made for this variable, i.e. the baseline value and at least one value after baseline (modified intention to treat analysis). Therefore, the total number of observations differs from the number of included participants. CGI-S: Clinical Global Impression-Severity, CSQ-4: Client Satisfaction Questionnaire, PHQ-9: Patient Health Questionnaire, SDS: Sheehan Disability Scale, sVMADRS: short version of the Montgomery Asberg Depression Rating Scale.

change as the physical distancing necessitated by the COVID-19 pandemic could lead to a sustained shift of mental health provision toward online treatment (Wind et al., 2020). Our recruitment difficulties somewhat limit the generalizability of our findings as patients who were highly motivated to use the intervention might have been more willing to pay for it. On the other hand, we have observed even higher usage intensities in previous RCTs where the intervention was provided at no cost to the participants (Klein et al., 2016; Meyer et al., 2015). It should also be noted that intervention usage was assessed by patients' self-reports and these may not be an accurate representation of actual adherence (Flett et al., 2019).

Furthermore, our study has an observational design and the observed decrease in depressive symptoms can therefore not be directly attributed to the use of the intervention. Observational studies are therefore considered lower quality evidence (Johnson et al., 2016). Numerous RCTs exist however that demonstrate the efficacy of deprexis (Twomey et al., 2020) and the pre-post effect size observed for the reduction of depressive symptoms in this study is comparable to the pre-post effect size reported in an RCT using deprexis in patients suffering from depressive symptoms of the same severity (Meyer et al., 2015). The observational design of our study offers the advantage of better generalizability of the findings to routine care because certain patients may not want to undergo randomization and therefore the study sample in an RCT may not be representative of the target population (Stuart et al., 2015). In fact, while the samples of our previous RCTs of deprexis were quite highly educated (Klein et al., 2016; Meyer et al., 2015), the level of education in the sample presented here comes closer to the general population with only one third having completed highest secondary education (Späth et al., 2017).

It could be argued that our intervention was a blended therapy because patients did not only use deprexis but also saw a clinician on a regular basis. In its broadest sense, blended therapy refers to any type of face-to-face treatment that is augmented with a digital intervention. More precisely, it can be subdivided into adjunctive treatments and highly integrated treatments (Schuster et al., 2020). The treatment format applied in our study can therefore be referred to as “adjunctive blended therapy”. Its results confirm results of RCTs where deprexis was offered in adjunct to psychotherapy, either in inpatient (Zwerenz et al., 2017) or outpatient setting (Berger et al., 2018): the pre-post effect size in our study was slightly larger than the pre-post effect sizes in the adjunctive therapy group in these RCTs.

In conclusion, our non-interventional study conducted in outpatient practices confirms results from numerous RCTs. Taken together, these data show that depressed patients use deprexis adequately with a large effect on their depressive symptomatology and no evidence of adverse events. The low recruitment rate however points to further needs regarding the dissemination of SMIs.

Contributors

BB and JPK designed the study and obtained funding. Patient recruitment was coordinated by BB. The statistical analyses were conducted by a contract research organization (ANFOMED GmbH, Möhrendorf, Germany) and confirmed by JPK. The results were interpreted by all authors. JPK wrote the manuscript with substantial input from SM and TB. All authors commented on the manuscript and approved the final version.

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Servier, Munich Germany. Servier is the distributor of the internet intervention “deprexis” and contributed to the design of the study, data collection and interpretation of the data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of competing interest

BBA is an employee of Servier Deutschland GmbH, Medical Affairs, Munich, Germany. JPK received funding for clinical trials (German Federal Ministry of Health, Servier - distributor of the internet intervention “deprexis”), payments for presentations on internet interventions (Servier), payments for workshops and books (Beltz, Elsevier, Hogrefe and Springer) on psychotherapy for chronic depression and on psychiatric emergencies.

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Data sharing statement

Individual participant data that underlie the results reported in this

article can be shared with researchers who provide a methodologically sound proposal to JPK. Proposals may be submitted up to 36 months following article publication.

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