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Impact of recruitment source in an RCT of an internet intervention for depression.

Cover Pages

Title

Effective across different settings: impact of recruitment source in the EVIDENT-study, a randomized controlled trial of an internet intervention for depressive symptoms.

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Running title: Impact of recruitment source in an RCT of an internet intervention for depression.

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Impact of recruitment source in an RCT of an internet intervention for depression.

Abstract

Objective: Examine whether the effects of internet interventions for depression generalize beyond participants recruited through the internet or the media.

Design: subgroup analysis of the results of a randomized, controlled, single-blind trial.

Setting: six diagnostic centers in Germany.

Participants: 1,013 people with mild to moderate depressive symptoms were recruited from clinical sources as well as internet forums, statuatory insurance companies, and other sources.

Interventions: either care-as-usual alone (control) or a 12-week internet intervention (Deprexis) plus usual care (intervention).

Main outcome measures: The primary outcome measure was self-rated depression severity (Patient Health Questionnaire: PHQ-9). Further measures ranged from demographic and clinical parameters to a measure of attitutes towards internet internetions (APOI).

Results: The recruitment source was only associated with very few of the examined demographic and clinical characteristics. Compared to participants recruited from clinical sources, participants recruited through insurance companies were more likely to be employed. Clinically recruited participants were as severely affected as those from other recruitment sources but more skeptical of internet interventions. The effectiveness of the intervention was not differentially associated with recruitment source (group by recruitment source interaction $F_{3,817}$=0.29, p = .83).

Conclusion: Our results support the hypothesis that the intervention we studied is effective across different recruitment sources.

Trial registration number: ClinicalTrials.gov NCT01636752.

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Strengths and limitations of this study

- Ours is the first trial to examine the effect of recruitment source on outcome.
- The large sample size makes detection of subgroup effects more likely.
- The absence of a subgroup effect does not prove that the effect applies to all subgroups.
- More randomized trials of internet interventions in clinical settings are needed.

Impact of recruitment source in an RCT of an internet intervention for depression.

Disclosures

Competing interests

JPK received funding for clinical trials (German Federal Ministry of Health, Servier), payments for presentations on internet interventions (Servier), payments for workshops and books (Beltz, Elsevier and Hogrefe) on psychotherapy for chronic depression and on psychiatric emergencies. BM is employed as research director at GAIA AG, the company that developed, owns, and operates the internet intervention "deprexis". MH is a consultant of Servier (distributor of the internet intervention "deprexis"). He was an invited speaker at several workshops and continuous education workshops over the last two years. All the other authors report no relationships with commercial interests.

Contributors

The principal investigators (TB, FH, JPK, BM and SM) designed the study and obtained funding. The EVIDENT study steering committee (TB, JPK, BM, SM, CS, JS) further developed the study design in collaboration with the EVIDENT study group (steering committee and Wolfgang Greiner, Bielefeld; MH; WL; Matthias Rose, Berlin) and CG. Patient recruitment was coordinated by the EVIDENT study group. JPK conducted the statistical analyses with substantial input from EV. The results were interpreted by the steering committee with substantial input from the study group and CG. JPK wrote the manuscript with substantial input from the steering committee and CG. All authors commented on the manuscript and approved the final version.

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Impact of recruitment source in an RCT of an internet intervention for depression.

Background

Numerous studies (Klein et al., 2016; Meyer et al., 2015; Moritz et al., 2015; Moritz et al., 2016) and meta-analyses (Andrews et al., 2010; Arnberg et al., 2014; Cuijpers et al., 2011; Johansson et al., 2012; Kuester et al., 2016; Olthuis et al., 2015) have shown that internet interventions are effective in the treatment of a broad array of psychiatric disorders, ranging from depression (Andrews et al., 2010; Cuijpers et al., 2011; Johansson et al., 2012) and anxiety (Andrews et al., 2010; Arnberg et al., 2014; Olthuis et al., 2015) to posttraumatic stress disorder (Kuester et al., 2016) and schizophrenia (Moritz et al., 2015; Moritz et al., 2016). However, most participants in these studies have been recruited through media advertisements (Andrews et al., 2010; Arnberg et al., 2014), so it remains unclear whether they are similar to those seeking face-to-face treatment in regular clinical settings (Andrews et al., 2010) and whether the effects for internet interventions generalize across different recruitment settings (Cuijpers et al., 2011).

Although some studies suggest that the promising results from efficacy studies can be transferred to routine clinical practice (Andersson et al., 2013; Hedman et al., 2014), one recent study (Gilbody et al., 2015) of two internet interventions in primary care reported null findings. This is not necessarily due to the fact that these interventions are not effective in primary care but might be explained by insufficient use of the interventions. No previous studies have directly examined whether differences in recruitment source are associated with the effectiveness of depression-focused internet interventions.

A better understanding of whether participants recruited from different sources differ in other important characteristics could help investigators avoid sampling bias or target specific clinical or demographic subgroups. Previous studies have addressed associations of recruitment source with patient characteristics in an internet clinic (Titov et al., 2010), in a trial of an internet intervention (Lindner et al., 2015) and in a trial of face-to-face psychotherapy for depression (Krusche et al., 2014). It might also be important to know if participants from certain recruitment sources are particularly open-minded towards internet interventions. But none of the previous studies have compared attitudes towards internet interventions across different recruitment sources.

Subgroup analyses examining associations between recruitment source and intervention effectiveness require large sample sizes (Wang et al., 2007). We have recently published one of the largest randomized trials of an internet intervention, the EVIDENT trial (Klein et al., 2016). Over one thousand participants were randomized for this trial that demonstrated the effectiveness of the intervention (Deprexis) for

mild to moderate depressive symptoms. In the EVIDENT trial, we also developed a novel questionnaire measuring positive and negative attitudes towards internet interventions (Schröder et al., 2015).

Using the EVIDENT trial data set, the current paper has two main objectives: firstly, we sought to examine whether recruitment source is systematically associated with various baseline parameters, including demographic and clinical characteristics as well as attitudes towards internet interventions. Secondly, we aimed to examine whether recruitment source is differentially associated with the effectiveness of the intervention. We also report on our general experiences with regard to recruiting participants from clinical settings in the EVIDENT trial.

Methods

The EVIDENT study is a multicenter (diagnostic interviews were conducted in five sites in Germany), randomized controlled trial (RCT). The trial was approved by the Ethics Committee of the German Psychological Association (DGPs SM 04_2012) and is registered with ClinicalTrials.gov (NCT01636752). The full study protocol has been published (Klein et al., 2013).

Participants

Participants were recruited via multiple settings and online informed consent was obtained prior to the baseline assessment. The main recruitment sources were internet forums for depression, magazines for members of statutory German health insurance companies and various inpatient and outpatient clinics, ranging from general practitioners' practices to psychiatrists' and psychotherapists' clinics, practices, and hospital settings.

Recruitment source was assessed by self-report; specifically, a combination of a multiple-choice question (clinical setting, internet forums, insurance company, other) and a free-text answer was used to identify the exact source via which each patient was recruited. One of the authors (CG) cross-checked the free-text answers against the multiple-choice answer and resolved any discrepancies through discussion with her local study team (CS and JPK).

The main inclusion criterion for the RCT was the presence of self-reported mild to moderate depressive symptoms, operationalized as a score between 5 and 14 on the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001). Eligible participants were between 18 and 65 years of age, had internet access and

were able to communicate in German. Participants with acute suicidality or a lifetime diagnosis of bipolar disorder or schizophrenia were excluded.

Interventions

Following a naturalistic and pragmatic design approach, care-as-usual was not influenced by the investigators. All participants were permitted to use any form of treatment, including antidepressant medication and psychotherapy. Participants were randomized equally (1:1) to the two groups (intervention or control). Participants in the control condition received only care-as-usual. They were offered access to the internet intervention after the last follow-up assessment. Participants in the intervention group received immediate access to the internet intervention (Deprexis) in addition to care-as-usual. Briefly, this program consists of modules covering content that is broadly consistent with CBT (e.g., cognitive restructuring, behavioral activation, acceptance and mindfulness, problem-solving) (Meyer et al., 2009). The intervention can be used with or without guidance by a clinician (Berger et al., 2011). In our trial, participants randomized to the intervention group with an initial PHQ-9 score between 10 and 14 received the guided version (e-mail support), those scoring between 5 and 9 on the PHQ-9 received the unguided version.

Outcome measures

The primary outcome for the RCT was change on the *Patient Health Questionnaire (PHQ-9)* (Kroenke et al., 2001). The internal consistency of the PHQ-9 based on the trial data was good (Cronbach's alpha = 0.83). The *Mini International Neuropsychiatric Interview (MINI)* (Sheehan et al., 1998) was used to assess the presence of a depressive disorder as well as to rule out a lifetime diagnosis of bipolar disorder or schizophrenia. Clinician-rated severity of depression was assessed with the 24-item version of the *Hamilton Depression Rating Scale* (Hamilton, 1960) (Cronbach's alpha = 0.79). The MINI and the HDRS-24 were administered via telephone by trained raters.

Attitudes towards internet interventions were assessed using a questionnaire that was developed during this trial, the *Attitudes towards Psychological Online Interventions Questionnaire (APOI)* (Schröder et al., 2015). The APOI is the first questionnaire that measures both positive and negative attitudes towards internet interventions in general. It comprises four subscales with scores ranging from 4 to 16, and these are labelled "skepticism and perception of risks", "confidence in effectiveness", "technologization threat" and "anonymity benefits". The total score ranges from 16 to 80 with higher scores reflecting a

more favorable attitude towards internet interventions. When calculating the total score, the polarity of the subscale scores for "skepticism and perception of risks" and "technologization threat" is reversed so that all subscales contribute equally to the total score. The internal consistency of the APOI in this sample is acceptable to good (Cronbach's alpha = 0.77).

Demographic details and treatment history were assessed with non-standardized questionnaires. We also employed a measure of health-related quality of life (*Short-Form Health Survey: SF-12)* (Ware, Jr. et al., 1996), the *Questionnaire for the Evaluation of Psychotherapeutic Processes (FEP-2)* (Lutz et al., 2009) and the *Web Screening Questionnaire (WSQ)*, a self-report instrument screening for frequent mental disorders (Donker et al., 2009).

Assessments

The PHQ-9 was administered via online questionnaires along with all the other self-ratings at baseline, after three months (post assessment) and after six months (follow-up assessment). Raters contacted participants for the MINI and the HDRS-24 at baseline and after three months.

Recruiter survey

We also invited the clinicians recruiting for our study to participate in an online survey. They were asked to provide demographic data and to complete two questionnaires: an unstandardized questionnaire that assessed their recruitment experience and the *Attitudes towards Psychological Online Interventions Questionnaire,* adapted for healthcare professionals *(APOI-HP)* (Schröder et al., 2016).

Statistical analysis

Statistical analyses were performed with SPSS 22 (IBM Corporation). We calculated univariate ANOVAs for continuous variables. Post-hoc tests were Bonferroni-corrected for multiple comparisons. For categorical variables, we calculated univariate multinomial logistic regression analyses. For the analysis of the effect of the recruitment source on treatment efficacy, we used linear mixed models (LMM), as they have the advantage of using all available data of each subject. Adjustment for baseline measure was chosen as this increases statistical power and accounts for regression to the mean. The analysis followed the intention-to-treat principle, which included all randomized participants. The outcome was analyzed as change from baseline with a random intercept for the participant. Time, study group, recruitment source and the interaction term group by recruitment source were entered as fixed effects and the

analysis was adjusted for the baseline depression severity. The hypothesis that the recruitment source influences the effect of the intervention on depressive symptoms was tested on the group by recruitment source interaction effect.

Results

Recruitment and participant flow

For the participant flow chart please refer to the report of the main results of this study (Klein et al., 2013). Briefly, 2020 participants were assessed for eligibilty, and 1007 (49.9%) were excluded. The most common exclusion criterion was exceeding a score of 14 on the PHQ-9 (748, 37.0%). Non-completion rates for the main outcome measure were 21.6% at post assessment (n = 219) and 24.6% at follow-up (n = 259). The non-completion rate did not differ between the different recruitment sources (chi^2_3= 4.34, p = .227 for the post assessment and chi^2_3= 2.06, p = .559 for the follow-up assessment).

Most participants (46%) self-identified as coming from the “other” recruitment source (see Table 1). The remaining participants came from statutory health insurance companies (27%), internet forums (17%) and clinical sources (10%). Inspection of the free-text answers revealed that most of the participants in the “other” category learned about the study through articles in the news media.

Participant characteristics

For descriptive and inferential statistics on the differences between the four recruitment sources, refer to Table 1 (demographic data) and Table 2 (clinical characteristics). Briefly, we did not find any statistically significant differences for a broad range of clinical characteristics including self- and clinician rated depression severity, psychosocial functioning and self-reported comorbid symptoms. Participants recruited through online forums were slightly more likely to suffer from dysthymia and participants from clinical settings and other sources were slightly more likely to report symptoms of panic disorder, but these differences were not statistically significant. We did find statistically significant differences between the recruitment sources for measures of resource use. Compared to participants recruited through insurance companies and other sources, participants recruited in clinical settings were more likely to be in psychiatric treatment (p < .05; OR vs. insurance 2.71, OR vs. other sources 1.70), psychotherapy (p < .01; OR vs. insurance 2.66, OR vs. other sources 1.99) and inpatient psychiatric treatment (p < .001; OR vs. insurance 4.06, OR vs. other sources 3.33, OR vs. internet forums 2.30). They also reported having had significantly more sick leave days (p < .001). We also observed differences for

demographic variables. Compared to participants recruited in a clinical setting, participants recruited through statutory health insurance companies were more likely to be employed full-time ($p < .01$) or part-time ($p < .01$). Participants from the different recruitment sources also differed in their attitudes to internet interventions (Table 3). Compared to participants recruited through insurance companies and other sources, those recruited in clinical settings had less favorable attitudes towards internet interventions ($p < .01$). In particular, they scored higher on skepticism and risk perception ($p < .01$) as well as technology disadvantages ($p < .01$). Participants recruited in clinical settings also differed from all the other groups in that they scored lower on perception of anonymity benefits ($p < .01$).

Intervention usage

A total of 509 participants were randomised to the intervention group. The mean number of sessions of at least 10 minutes duration was 8.32 (*SD* = 4.71), the mean total usage time was 429.70 (*SD* = 294.0) minutes (about seven hours). Participants from the different recruitment sources did not differ with respect to the number of sessions ($F_{3,481} = 0.47$, $p = .70$) or the total usage time ($F_{3,481} = 0.51$, $p = .70$).

Symptom change

As reported previously (Klein et al., 2016), the intervention had a significant effect on the main outcome, change in PHQ-9 scores from baseline to post and follow-up. Whereas depressive symptoms decreased in both groups, changes in PHQ-9 differed significantly (main effect of group: $F_{1,823} = 21.84$, $p < .001$) between groups. In the intervention group, PHQ-9 scores decreased by 1.40 (95% CI 0.81—1.99) points more than in the CAU group, on average. We also observed a main effect of recruitment source on PHQ change, which was marginally significant ($F_{3,817} = 2.58$, $p = .053$). Average symptom change was greater in those recruited from clinical sources than those recruited via internet forums (1.33; 95%, CI -0.30—2.70; Bonferroni corrected $p = .059$). The interaction term (group assignment by recruitment source) was not statistically significant ($F_{3,817} = 0.29$, $p = .83$), indicating that treatment response was unrelated to recruitment source (Table 4).

As a sensitivity analysis, we reran the analysis of the interaction effect with a binary subgroup definition. Here we summarized the following recruitment sources as non-clinical: statutory health insurance companies, internet forums and “other” recruitment sources. Again, we found a significant main effect of recruitment source on PHQ-change ($F_{1,834} = 5.45$, $p = .02$). Symptom change was greater in those recruited from clinical sources compared to those not recruited from clinical sources (1.50; 95%, CI

0.33—2.68). The interaction term (group assignment by binary recruitment source) was not statistically significant ($F_{1,834}$= 1.66, p = .20) confirming the result of the main subgroup analysis above.

We also conducted a sensitivity analysis with the binary outcome "minimally clinically important PHQ-change" as the dependent variable (binary logistic regression: chi^2_3 = 19.749, p < .001, Nagelkerkes r^2 = .031). A minimally clinically important individual PHQ-9 improvement was defined as five point reduction (Lowe et al., 2004). In keeping with the results of the previously reported analyses we found a main effect of group (B = 1.18 (SE .51) p = .021) but the group by recruitment source interaction term was not statistically significant (B = -0.16 (SE .16) p = .31).

Recruiter characteristics

A total of 89 persons who supported our recruitment efforts in clinical settings (the recruiters) were contacted via e-mail for an online survey. Of these, 48 completed the survey (54%). They were mostly female (69%) and their mean age was 44.06 (SD 12.17). Almost half of them reported working in an inpatient setting (42%), mostly as psychotherapists (50%), specialists in psychosomatic medicine (33%) and psychiatry (22.9%). Recruiters could name multiple fields of work and, therefore, the total sum exceeds 100%. Recruiters also completed a questionnaire inquiring about their experiences with regard to the recruitment process. Here, 40% reported that they often forgot to talk with their patients about the study. 25% wrote they did not have the time to talk with their patients about the study or that their patients' symptoms were too severe to participate in the study. Only 12.5% of respondents reported inadequate computer literacy as a barrier to participating in the study. On the APOI, the recruiters had a total mean score of 51.23 (SD 12.17) and the following subscale mean scores (SD): skepticism and risk perception 11.14 (2.55), confidence in effectiveness 16.08 (1.92) perceived technology disadvantages 14.50 (SD 2.34) and perception of anonymity benefits 12.64 (2.47).

Discussion

Principal findings

This study examined associations of recruitment source with participant characteristics and effectiveness in a trial of an internet intervention for depressive symptoms. We found few demographic or clinical differences among participants recruited from different sources and no association of recruitment source with treatment effect. To our knowledge, this is the first study that examines the association of the recruitment source with the effectiveness of an internet intervention. While we have found that the

between-group effect is the same across recruitment sources, we did find that the within-group effect is smaller in those recruited via internet forums than in those recruited via other settings. This differential within-group effect was only marginally statistically significant though and should thus be replicated in other studies before conclusion can be drawn from this finding. If confirmed in other studies, these findings might imply that the recruitment source is a predictor of symptom change but does not have a moderating effect on the effectiveness of the intervention.

Comparison with other studies

Some of the findings regarding clinical characteristics contrast with results from a previous study (Lindner et al., 2015), which found somewhat more severe symptoms in patients recruited through clinical settings. Participants recruited in clinical settings in our study were more likely to be on sick-leave, suggesting that despite similar current symptom severity, their symptom-related psychosocial impairment in the six months preceding randomization might have been greater. Even though participants recruited in clinical settings did not differ from others in depression severity or quality of life, they were about twice as likely to be in psychiatric treatment, compared to participants recruited via health insurance companies (OR 2.71) or other sources, such as news media (OR 1.70). This might indicate that internet interventions reach people who chose not to seek treatment through more conventional means in spite of substantial symptom severity (Moritz et al., 2012).

We have found that participants recruited through insurance companies were more likely to be employed. Also we observed a significant between groups difference regarding level of education. These findings might orient researchers wishing to recruit participants with certain demographics as it has been noted that participants in internet studies as well as outpatient treatment centers are more highly educated than the general population (Titov et al., 2010).

Participants recruited through clinical settings had a less favorable view of internet interventions compared to the other groups. The recruiters working in these clinical settings viewed internet interventions less favorably than the participants. Understandably, patients engaging with psychiatric or psychotherapeutic treatment and clinical treatment providers may regard internet based treatments with somewhat greater skepticism. Interestingly, recruiters for our study had a more positive view of internet interventions than psychotherapists recruited through professional associations for psychotherapists who were surveyed in a separate study (Schröder et al., 2016). This might be due to

sampling bias: clinicians who are skeptical of internet interventions are less likely to recruit for a study of such an intervention.

Limitations of the study

In spite of this relatively positive attitude, the 89 recruiters only recruited 105 participants for this trial that were eligible to participate and could thus be randomized. This figure must be interpreted with caution though as we could not link study participants to individual recruiters. Therefore, we do not know whether the recruiters surveyed here actually recruited the participants in this study that self-identified as clinically recruited. Still, these figures do suggest that it is more difficult to recruit for an internet intervention through clinical settings compared to recruitment through the media and the internet. These recruitment difficulties were not related to characteristics of the internet intervention but rather to more general problems with recruiting for studies in a busy clinical routine.

There are some further limitations to consider when interpreting our results. The most common recruitment source was “other”, and most of these participants learned about our study through news media. The clinical recruitment sources were heterogeneous. Most of the clinical recruiters self-identified as psychotherapists. Our results may therefore have been different if we had recruited in general practice. Also, our sample reported mild to moderate depressive symptoms and it is therefore unclear if our results also extend to people with more severe depressive symptoms or other primary mental health complaints. The inclusion of only mild and moderately depressed subjects might also have limited our ability to detect baseline differences in clinical characteristics.

Furthermore, the absence of an interaction effect in our subgroup analysis does not necessarily mean that the treatment effect applies to all subgroups (Wang et al., 2007). Statistical power is considerably lower for interaction analyses compared to the main effect analysis, particularly if the subgroups are not identical in size as in our study (Brookes et al., 2004). Inspection of Table 4 suggests that a differential treatment effect might have attained statistical significance in an even larger sample. We have previously reported that the internet intervention was less efficacious in mild to moderate depressives who also received psychiatric or psychotherapeutic treatment (Klein et al., 2016). Internet interventions may therefore confer the greatest benefit for individuals who are not in specialized psychiatric or psychotherapeutic care.

Impact of recruitment source in an RCT of an internet intervention for depression.

Conclusion

We conclude participants recruited through the internet or the media have been found to be as severely affected as patients seen in regular care. Also we found that the internet intervention studied here (Deprexis) appears to be equally effective for mildly to moderately depressed participants regardless of their recruitment source. This adds to the growing literature that the impressive evidence of internet interventions for psychiatric disorders might also extend to clinical settings. Still, more studies are needed that only recruit in clinical settings before this can be said with more certainty.

Impact of recruitment source in an RCT of an internet intervention for depression.

Tables and Figures

Table 1: Differences in demographic data between different recruitment sources.

	Recruitment Source												Statistics		
	(1) Clinical			(2) Internet Forums			(3) Insurance			(4) Other			Between groups		
Demographic characteristics	N	M	SD	N	M	SD	N	M	SD	N	M	SD	df	F	p
Age	105	41.58	11.930	171	41.89	11.239	271	43.32	9.777	466	43.23	11.327	3,1009	1.250	.290
Marital Status	N	N	%	N	N	%	N	N	%	N	N	%	df	chi^2	p
Married		36	34.3%		57	33.3%		131	48.3%		201	43.1%			
Commited relation	105	24	22.9%	171	32	18.7%	271	44	16.2%	466	89	19.1%	15	30.289	.011
Single		29	27.6%		51	29.8%		51	18.8%		116	24.9%			
Education status	N	N	%	N	N	%	N	N	%	N	N	%	df	chi^2	p
Highest secondary	105	52	49.5%	171	87	50.9%	271	118	43.5%	466	263	56.4%			
Higher secondary	105	15	14.3%	171	38	22.2%	271	54	19.9%	466	65	13.9%	18	37.205	.005
Middle secondary	105	27	25.7%	171	35	20.5%	271	84	31.0%	466	97	20.8%			
Employment status	N	N	%	N	N	%	N	N	%	N	N	%	df	chi^2	p
Full-time		44	41.9%		65	38.0%		136	50.2%		189	40.6%			
Part time	105	17	16.2%	171	32	18.7%	271	75	27.7%	466	103	22.1%	9	30.239	< .001
Other		18	17.1%		27	15.8%		24	8.9%		62	13.3%			

Impact of recruitment source in an RCT of an internet intervention for depression.

Table 2: Differences in clinical characteristics between different recruitment sources.

	Recruitment Source												Statistics		
	(1) Clinical			(2) Internet Forum			(3) Insurance			(4) Other			Between groups		
Clinical characteristics	N	M	SD	N	M	SD	N	M	SD	N	M	SD	*df*	*F*	*p*
PHQ	105	10.06	2.60	171	10.21	2.44	271	10.40	2.39	466	10.30	2.38	3,1009	0.570	.635
PHQ suicidality item		1.30	0.483		1.23	0.451		1.21	0.406		1.27	0.461		1.905	.127
SF-12 PH	102	46.42	9.52	169	46.83	9.91	262	47.64	9.06	456	48.05	9.44	3,985	1.248	.291
SF-12 MH		30.11	6.96		31.39	8.45		31.49	7.34		31.51	7.69		0.987	.398
FEP-2	105	2.93	0.47	171	2.99	0.47	271	2.92	0.46	466	2.918	0.45	3,1009	1.079	.357
HRSD		17.47	7.49		17.49	7.58		16.14	7.47		16.73	7.41		1.477	.219
Diagnosis	N	N	%	N	N	%	N	N	%	N	N	%	df	chi^2	p
Dysthymia		33	31.4%		77	45.0%		100	36.9%		166	35.6%		6.494	.090
Depressive Episode		36	34.3%		47	27.5%		75	27.7%		132	28.3%		1.895	.594
More than 5 episodes	105	36	34.3%	171	66	38.6%	271	99	36.5%	466	192	41.2%	3	2.624	.453
Panic d/o (WSQ)		40	38.1%		47	27.5%		75	27.7%		159	34.1%		6.676	.083
Social phobia (WSQ)		46	43.8%		80	46.8%		127	46.9%		221	47.4%		0.451	.930
Alcohol use d/o (WSQ)		4	3.8%		6	3.5%		11	4.1%		31	6.7%		4.155	.245
Resource use	N	N	%	N	N	%	N	N	%	N	N	%	df	chi^2	p
General practitioner		92	87.6%		141	82.5%		240	88.6%		397	85.2%		3.703	.295
Psychiatrist		44	41.9%		72	42.1%		57	21.0%		139	29.8%		28.665	< .001
Psychotherapist		52	49.5%		73	42.7%		73	26.9%		155	33.3%	3	22.579	< .001
Neurologist	105	20	19.0%	171	38	22.2%	271	39	14.4%	466	62	13.3%		8.758	.033
Inpatient psychiatry		19	18.1%		15	8.8%		14	5.2%		29	6.2%		20.345	< .001
		M	SD		M	SD		M	SD		M	SD	*df*	*F*	*p*
Sick leave days		40.13	66.675		29.99	53.542		15.72	36.411		20.15	43.402	3,1009	8.814	< .001

Impact of recruitment source in an RCT of an internet intervention for depression.

Table 3: Differences in attitude to psychological internet intervention.

	Recruitment Source												Statistics		
	(1) Clinical			(2) Internet Forum			(3) Insurance			(4) Other			Between groups		
APOI score	N	M	SD	N	M	SD	N	M	SD	N	M	SD	df	F	p
Skepticism and Risk Perception	105	9.86	2.380	169	9.88	2.254	270	9.36	2.278	460	9.30	2.313	3,1009	3.861	0.009
Confidence in Effectiveness		16.43	2.148		16.44	2.140		16.66	2.027		16.74	2.150		1.186	0.314
Technologization Threat		12.47	2.122		12.04	2.502		11.52	2.406		11.63	2.533		4.908	0.002
Anonymity Benefits		11.48	2.879		12.62	2.605		12.70	3.067		12.47	3.191		4.373	0.005
Total		53.58	6.365		55.14	6.719		56.47	6.832		56.28	6.955		5.850	0.001

Impact of recruitment source in an RCT of an internet intervention for depression.

Table 4: Group effect and group by recruitment source interaction effect on estimated mean change in depressive symptoms (PHQ-9) from baseline to post and follow-up and minimally clinically relevant PHQ-change at post assessment.

Recruitment source	Group	Estimated change				Effect Size		Minimally clinically important PHQ change		Effect size	
		Mean	SE	95% CI		d	95% CI	N	%	NNT	95% CI
Main effect of group		$F_{1,823}$ = 21.84, p < .001						B = 1.18 (SE .51) p = .021			
All (n = 1013)	Intervention (n = 509)	2.53	.221	2.09	2.96	0.37	0.06 – 0.67	143	28.1	9	6 – 15
	Control (n = 504)	1.13	.222	0.69	1.56			83	16.5		
Group by recruitment source interaction		$F_{3,817}$=0.29, p = .83						B = -0.16 (SE .16) p = .31			
Clinical (n = 105)	Intervention (n = 42)	2.900	.547	1.826	3.973	0.26	-0.52 – 1.03	17	29.8	5	-3 – 107
	CAU (n = 38)	1.994	.585	0.845	3.142			8	16.7		
Internet forums (n = 171)	Intervention (n = 63)	1.794	.468	.874	2.714	0.38	-0.26 – 1.01	23	28.0	5	3 – 15
	CAU (n = 62)	0.428	.458	-0.471	1.328			9	10.1		
Insurance (n = 271)	Intervention (n = 106)	2.827	.359	2.122	3.532	0.46	-0.04 – 0.95	40	29.9	7	4 – 39
	CAU (n = 113)	1.135	.353	0.442	1.828			26	19.0		
Other (n = 466)	Intervention (n = 184)	2.584	.278	2.039	3.129	0.44	0.05 – 0.82	63	26.7	8	5 – 28
	CAU (n = 186)	0.942	.279	0.394	1.490			40	17.4		

Impact of recruitment source in an RCT of an internet intervention for depression.

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Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	7
	2b	Specific objectives or hypotheses	8
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n.a.
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n.a.
Sample size	7a	How sample size was determined	10 / 15
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n.a.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Available in main publication
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Available in main publication
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	9
	11b	If relevant, description of the similarity of interventions	n.a.
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup	10

		analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Available in main publication
	14b	Why the trial ended or was stopped	n.a.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	17
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	20
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	20
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	20
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Available in main publication
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	8
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	5

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Does recruitment source moderate treatment effectiveness? A subgroup analysis from the EVIDENT study, a randomised controlled trial of an internet intervention for depressive symptoms.

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Impact of recruitment source in an RCT of an internet intervention for depression.

Cover Pages

Title

Does recruitment source moderate treatment effectiveness? A subgroup analysis from the EVIDENT study, a randomised controlled trial of an internet intervention for depressive symptoms.

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Running title: Impact of recruitment source in an RCT of an internet intervention for depression.

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Impact of recruitment source in an RCT of an internet intervention for depression.

Abstract

Objective: Examine whether the effects of internet interventions for depression generalize beyond participants recruited through the internet or the media.

Design: subgroup analysis of the results of a randomized, controlled, single-blind trial.

Setting: five diagnostic centers in Germany.

Participants: 1,013 people with mild to moderate depressive symptoms were recruited from clinical sources as well as internet forums, statuatory insurance companies, and other sources.

Interventions: either care-as-usual alone (control) or a 12-week internet intervention (Deprexis) plus usual care (intervention).

Main outcome measures: The primary outcome measure was self-rated depression severity (Patient Health Questionnaire: PHQ-9). Further measures ranged from demographic and clinical parameters to a measure of attitutes towards internet interventions (APOI).

Results: The recruitment source was only associated with very few of the examined demographic and clinical characteristics. Compared to participants recruited from clinical sources, participants recruited through insurance companies were more likely to be employed. Clinically recruited participants were as severely affected as those from other recruitment sources but more skeptical of internet interventions. The effectiveness of the intervention was not differentially associated with recruitment source (treatment by recruitment source interaction $F_{3,824} = 0.28$, $p = .84$).

Conclusion: Our results support the hypothesis that the intervention we studied is effective across different recruitment sources.

Trial registration number: ClinicalTrials.gov NCT01636752.

Impact of recruitment source in an RCT of an internet intervention for depression.

Strengths and limitations of this study

- Ours is the first trial to examine the effect of recruitment source on outcome.
- The large sample size makes detection of subgroup effects more likely.
- The absence of a subgroup effect does not prove that the effect applies to all subgroups.
- More randomized trials of internet interventions in clinical settings are needed.

Impact of recruitment source in an RCT of an internet intervention for depression.

Background

Numerous studies [1-4] and meta-analyses [5-10] have shown that internet interventions are effective in the treatment of a broad array of psychiatric disorders, ranging from depression [5-7] and anxiety [7-9] to posttraumatic stress disorder [10] and schizophrenia [1,2]. However, most participants in these studies have been recruited through media advertisements [7,9], so it remains unclear whether they are similar to those seeking face-to-face treatment in regular clinical settings [7] and whether the effects for internet interventions generalize across different recruitment settings [5].

Although some studies suggest that the promising results from efficacy studies can be transferred to routine clinical practice [11,12], one recent study [13] of two internet interventions in primary care reported null findings. This is not necessarily due to the fact that these interventions are not effective in primary care but might be explained by insufficient use of the interventions. No previous studies have directly examined whether differences in recruitment source are associated with the effectiveness of depression-focused internet interventions.

A better understanding of whether participants recruited from different sources differ in other important characteristics could help investigators avoid sampling bias or target specific clinical or demographic subgroups. Previous studies have addressed associations of recruitment source with patient characteristics in an internet clinic [14], in a trial of an internet intervention [15] and in a trial of face-to-face psychotherapy for depression [16]. It might also be important to know if participants from certain recruitment sources are particularly open-minded towards internet interventions. But none of the previous studies have compared attitudes towards internet interventions across different recruitment sources.

Subgroup analyses examining associations between recruitment source and intervention effectiveness require large sample sizes [17]. We have recently published one of the largest randomized trials of an internet intervention, the EVIDENT trial [3]. Over one thousand participants were randomized for this trial that demonstrated the effectiveness of the intervention (Deprexis) for mild to moderate depressive symptoms. In the EVIDENT trial, we also developed a novel questionnaire measuring positive and negative attitudes towards internet interventions [18].

Using the EVIDENT trial data set, the current paper has two main objectives: firstly, we sought to examine whether recruitment source is systematically associated with various baseline parameters,

including demographic and clinical characteristics as well as attitudes towards internet interventions. Secondly, we aimed to examine whether recruitment source is differentially associated with the effectiveness of the intervention. We also report on our general experiences with regard to recruiting participants from clinical settings in the EVIDENT trial.

Methods

The EVIDENT study is a multicentre (diagnostic interviews were conducted in five sites in Germany), randomized controlled trial (RCT). The trial was approved by the Ethics Committee of the German Psychological Association (DGPs SM 04_2012) and is registered with ClinicalTrials.gov (NCT01636752). The full study protocol has been published [19].

Participants

Participants were recruited via multiple settings and online informed consent was obtained prior to the baseline assessment. The main recruitment sources were internet forums for depression, magazines for members of statutory German health insurance companies and various inpatient and outpatient clinics, ranging from general practitioners' practices to psychiatrists' and psychotherapists' clinics, practices, and hospital settings.

Recruitment source was assessed by self-report; specifically, a combination of a multiple-choice question (clinical setting, internet forums, insurance company, other) and a free-text answer was used to identify the exact source via which each patient was recruited. One of the authors (CG) cross-checked the free-text answers against the multiple-choice answer and resolved any discrepancies through discussion with her local study team (CS and JPK).

The main inclusion criterion for the RCT was the presence of self-reported mild to moderate depressive symptoms, operationalized as a score from 5 to 14 on the Patient Health Questionnaire-9 (PHQ-9) [20]. Eligible participants were from 18 to 65 years of age, had internet access and were able to communicate in German. Participants with acute suicidality or a lifetime diagnosis of bipolar disorder or schizophrenia were excluded.

Interventions

Following a naturalistic and pragmatic design approach, care-as-usual was not influenced by the investigators. All participants were permitted to use any form of treatment, including antidepressant

medication and psychotherapy. Participants were randomized equally (1:1) to the two groups (intervention or control). Participants in the control condition received only care-as-usual (hereafter referred to as the CAU group). They were offered access to the internet intervention after the last follow-up assessment. Participants in the intervention group received immediate access to the internet intervention (Deprexis) in addition to care-as-usual. Briefly, this program consists of modules covering content that is broadly consistent with CBT (e.g., cognitive restructuring, behavioural activation, acceptance and mindfulness, problem-solving) [21]. The intervention can be used with or without guidance by a clinician [22]. In our trial, participants randomized to the intervention group with an initial PHQ-9 score from 10 to 14 received the guided version (e-mail support); those scoring from 5 to 9 on the PHQ-9 received the unguided version.

Outcome measures

The primary outcome for the RCT was change on the *Patient Health Questionnaire (PHQ-9)* [20]. The internal consistency of the PHQ-9 based on the trial data was good (Cronbach's alpha = 0.83). The *Mini International Neuropsychiatric Interview (MINI)* [23] was used to assess the presence of a depressive disorder as well as to rule out a lifetime diagnosis of bipolar disorder or schizophrenia. Clinician-rated severity of depression was assessed with the 24-item version of the *Hamilton Depression Rating Scale* [24] (Cronbach's alpha = 0.79). The MINI and the HDRS-24 were administered via telephone by trained raters.

Attitudes towards internet interventions were assessed using a questionnaire that was developed during this trial, the *Attitudes towards Psychological Online Interventions Questionnaire (APOI)* [18]. The APOI is the first questionnaire that measures both positive and negative attitudes towards internet interventions in general. It comprises four subscales with scores ranging from 4 to 20, and these are labelled "scepticism and perception of risks", "confidence in effectiveness", "technologization threat" and "anonymity benefits". The total score ranges from 16 to 80 with higher scores reflecting a more favourable attitude towards internet interventions. When calculating the total score, the polarity of the subscale scores for "scepticism and perception of risks" and "technologization threat" is reversed so that all subscales contribute equally to the total score. The internal consistency of the APOI in this sample is acceptable to good (Cronbach's alpha = 0.77).

Demographic details and treatment history were assessed with non-standardized questionnaires. We also employed the following self-rating scales: a measure of health-related quality of life (*Short-Form*

Health Survey: SF-12) [25] that covers physical health related qualitiy of life (SF-12 PH) and mental health related quality of life (SF-12 MH); a broad symptom measure covering dimensions ranging from general well-being to interpersonal relationships (*Questionnaire for the Evaluation of Psychotherapeutic Processes - FEP-2)* [26] and the *Web Screening Questionnaire (WSQ)*, an instrument screening for frequent mental disorders [27].

Assessments

The PHQ-9 was administered via online questionnaires along with all the other self-ratings at baseline, after three months (post assessment) and after six months (follow-up assessment). Raters contacted participants for the MINI and the HDRS-24 at baseline and after three months.

Recruiter survey

We also invited the clinicians recruiting for our study to participate in an online survey. They were asked to provide demographic data and to complete two questionnaires: an unstandardized questionnaire that assessed their recruitment experience and the *Attitudes towards Psychological Online Interventions Questionnaire,* adapted for healthcare professionals *(APOI-HP)* [28].

Statistical analysis

Statistical analyses were performed with SPSS 22 (IBM Corporation). We calculated univariate ANOVAs for continuous variables. Post-hoc tests were Bonferroni-corrected for multiple comparisons. For categorical variables, we calculated univariate multinomial logistic regression analyses. Effect sizes are presented as Cohen's d for continuous data and numbers needed to treat (NNT) for dichotomous data.

For the analysis of the effect of the recruitment source on treatment effectiveness, we used linear mixed models (LMM), as they have the advantage of using all available data of each subject. They also offer the opportunity to choose an appropriate covariance structure reflecting the potential dependence due to repeated measurements [29]. Adjustment for baseline measure was chosen as this accounts for regression to the mean [30]. The analysis followed the intention-to-treat principle, which included all randomized participants. No missing values were substituted as LMMs based on all observed data are valid and unbiased methods for missing at random (MAR) data [31].

The outcome was analysed as change from baseline with a random intercept for the participant. Time, treatment group, recruitment source and the interaction term treatment by recruitment source were

entered as fixed effects. We chose an autoregressive covariance structure and allowed variances to vary between assessment points. The choice was based on Akaike's Information Criterion (AIC) from a fixed set of candidate structures, namely a first order autoregressive (AR1), or scaled identity structure or heterogeneous versions thereof. The hypothesis that the recruitment source influences the effect of the intervention on depressive symptoms was tested on the treatment by recruitment source interaction. Here, the effect of the intervention is defined as the mean difference between average change in outcome for the intervention group minus average change in outcome for the CAU group (the difference in differences). The subgroup analysis had been pre-specified in the study protocol [19].

Results

Recruitment and participant flow

For the participant flow chart please refer to the report of the main results of this study [19]. Briefly, 2020 participants were assessed for eligibilty, and 1007 (49.9%) were excluded. The most common exclusion criterion was exceeding a score of 14 on the PHQ-9 (748, 37.0%). Non-completion rates for the main outcome measure were 21.6% at post assessment (*n* = 219) and 24.6% at follow-up (*n* = 259). The non-completion rate did not differ between the different recruitment sources (chi^2_3= 4.34, p = .227 for the post assessment and chi^2_3= 2.06, p = .559 for the follow-up assessment).

Most participants (46%) self-identified as coming from the “other” recruitment source (see Table 1). The remaining participants came from statutory health insurance companies (27%), internet forums (17%) and clinical sources (10%). Inspection of the free-text answers revealed that most of the participants in the “other” category learned about the study through articles in the news media.

Participant characteristics

For descriptive and inferential statistics on the differences between the four recruitment sources, refer to Table 1 (demographic data) and Table 2 (clinical characteristics). Briefly, we did not find any statistically significant differences for a broad range of clinical characteristics including self- and clinician rated depression severity, psychosocial functioning and self-reported comorbid symptoms. Participants recruited through online forums were slightly more likely to suffer from dysthymia and participants from clinical settings and other sources were slightly more likely to report symptoms of panic disorder, but these differences were not statistically significant. We did find statistically significant differences between the recruitment sources for measures of resource use. Compared to participants recruited

through insurance companies and other sources, participants recruited in clinical settings were more likely to be in psychiatric treatment ($p < .05$; odds ratio [OR] vs. insurance 2.71, OR vs. other sources 1.70), psychotherapy ($p < .01$; OR vs. insurance 2.66, OR vs. other sources 1.99) and inpatient psychiatric treatment ($p < .001$; OR vs. insurance 4.06, OR vs. other sources 3.33, OR vs. internet forums 2.30). They also reported having had significantly more sick leave days ($p < .001$; d vs. insurance 0.52, d vs. other sources 0.41).

We also observed differences for demographic variables. Compared to participants recruited in a clinical setting, participants recruited through statutory health insurance companies were more likely to be employed full-time ($p < .01$; OR 2.23) or part-time ($p < .01$; OR 3.19). Participants from the different recruitment sources also differed in their attitudes to internet interventions (Table 3). Compared to participants recruited through insurance companies and other sources, those recruited in clinical settings had less favourable attitudes towards internet interventions ($p < .01$; d vs. insurance 0.43, d vs. other sources 0.40). In particular, they scored higher on technologization threat ($p < .01$; d vs. insurance companies 0.41, d vs. other sources 0.34) and lower on anonymity benefits ($p < .01$; d vs. internet forums 0.42, d vs. insurance companies 0.41, d vs. other sources 0.32).

Intervention usage

A total of 509 participants were randomised to the intervention group. The mean number of sessions of at least 10 minutes duration was 8.32 (*SD* = 4.71), the mean total usage time was 429.70 (*SD* = 294.0) minutes (about seven hours). Periods of inactivity of 5 min or longer were subtracted in the computation of the total usage time. Participants from the different recruitment sources did not differ with respect to the number of sessions ($F_{3,481} = 0.47$, $p = .70$) or the total usage time ($F_{3,481} = 0.51$, $p = .70$).

Primary and secondary outcomes

As reported previously [3], the intervention had a significant effect on the main outcome, change in PHQ-9 scores from baseline to post and follow-up. Whereas depressive symptoms decreased in both groups, changes in PHQ-9 differed significantly (main effect of treatment: $F_{1,829} = 23.05$, $p < .001$) between groups. In the intervention group, PHQ-9 scores decreased by 1.43 (95% CI 0.85 — 2.02) points more than in the CAU group, on average. Both the main effect of recruitment source ($F_{3,825} = 2.61$, $p = .051$) and the interaction term (treatment assignment by recruitment source) were not statistically significant ($F_{3,824} = 0.28$, $p = .84$)(Table 4).

The analysis of the secondary outcomes (HRSD, SF-12 and FEP-2) mostly yielded the same pattern of results (Table 5). The main effect of group was statistically significant for all secondary outcomes except for physicial health-related qualtiy of life (SF-12 PH). The main effect of recruitment source was significant for mental health related quality of life (p = .011) with patients recruited via internet forums reporting smaller improvements compared to participants recruited from clinical settings (-3.82; 95%, CI -7.18 — -0.47; Bonferroni corrected p = .016) and participants recruited from other sources (-2.57; 95%, CI -4.99 — -0.15; Bonferroni corrected p = .030). The interaction term (treatment assignment by recruitment source) was not statistically significant for any of the secondary outcomes.

Sensitivity analyses

As a sensitivity analysis for the primary outcome, we reran the analysis of the interaction with a binary subgroup definition. Here we summarized the following recruitment sources as non-clinical: statutory health insurance companies, internet forums and "other" recruitment sources. Here, we replicated the significant main effect of treatment ($F_{1,834}$ = 7.94, p < .01) and found a significant main effect of recruitment source on change of PHQ-9 ($F_{1,834}$ = 5.45, p = .02). Symptom change was greater in those recruited from clinical sources compared to those not recruited from clinical sources (1.50; 95%, 0.33 — 2.68). The interaction term (treatment by binary recruitment source) was not statistically significant ($F_{1,834}$= 1.66, p = .20) confirming the result of the main subgroup analysis above.

We also conducted a sensitivity analysis with the binary outcome "minimally clinically important change of PHQ-9" as the dependent variable (binary logistic regression: chi^2_3 = 19.749, p < .001, Nagelkerkes r^2 = .031). A minimally clinically important individual PHQ-9 improvement was defined as five point reduction [32]. In keeping with the results of the previously reported analyses we found a main effect of treatment (B = 1.18 (SE .51), p = .021), no main effect of recruitment source (B = 0.08 (SE .13), p = 0.53) and the treatment by recruitment source interaction term was not statistically significant (B = -0.16 (SE .16), p = .31).

In a final sensitivity analysis we used multiple imputation (50 imputations) to estimate missing scores by evaluating the relationships between observed and missing scores as well as baseline scores. The results were essentially the same as for the main analysis (main effect of treatment: $F_{1,1004}$ = 111.52, p < .001; main effect of recruitment source on change of PHQ-9: $F_{3,1004}$ = 2.547, p = .055; treatment assignment by recruitment source interaction: $F_{3,1004}$ = 0.45, p = .72).

Recruiter characteristics

A total of 89 persons who supported our recruitment efforts in clinical settings (the recruiters) were contacted via e-mail for an online survey. Of these, 48 completed the survey (54%). They were mostly female (69%) and their mean age was 44.06 (SD 12.17). Almost half of them reported working in an inpatient setting (42%), mostly as psychotherapists (50%), specialists in psychosomatic medicine (33%) and psychiatry (22.9%). Recruiters could name multiple fields of work and, therefore, the total sum exceeds 100%. Recruiters also completed a questionnaire inquiring about their experiences with regard to the recruitment process. Here, 40% reported that they often forgot to talk with their patients about the study. 25% wrote they did not have the time to talk with their patients about the study or that their patients' symptoms were too severe to participate in the study. Only 12.5% of respondents reported inadequate computer literacy as a barrier to participating in the study. On the APOI, the recruiters had a total mean score of 51.23 (SD 12.17) and the following subscale mean scores (SD): scepticism and risk perception 11.14 (2.55), confidence in effectiveness 16.08 (1.92) perceived technology disadvantages 14.50 (SD 2.34) and perception of anonymity benefits 12.64 (2.47).

Discussion

Principal findings

This study examined associations of recruitment source with participant characteristics and effectiveness in a trial of an internet intervention for depressive symptoms. We found few demographic or clinical differences among participants recruited from different sources. To our knowledge, this is the first study that examines the association of the recruitment source with the effectiveness of an internet intervention. Here, we found no moderating influence of the recruitment source on the treatment effect. We did find an indication however that the recruitment source might predict course of depressive symptoms independent of treatment group assignment. Decrease of symptoms was greater in those recruited from clinical sources than in those recruited via other settings. This finding was only statistically significant in one of the sensitivity analysis though and should thus be replicated in other studies before firm conclusions can be drawn from this finding.

Comparison with other studies

Some of the findings regarding clinical characteristics contrast with results from a previous study [15], which found somewhat more severe symptoms in patients recruited through clinical settings.

Participants recruited in clinical settings in our study were more likely to be on sick-leave, suggesting that despite similar current symptom severity, their symptom-related psychosocial impairment in the six months preceding randomization might have been greater. Even though participants recruited in clinical settings did not differ from others in depression severity or quality of life, they were about twice as likely to be in psychiatric treatment, compared to participants recruited via health insurance companies (OR 2.71) or other sources, such as news media (OR 1.70). This might indicate that internet interventions reach people who chose not to seek treatment through more conventional means in spite of substantial symptom severity [33].

We have found that participants recruited through insurance companies were more likely to be employed. Also we observed a significant between groups difference regarding level of education. These findings might provide some orientation for researchers wishing to recruit participants with certain demographics as it has been noted that participants in internet studies as well as outpatient treatment centres are more highly educated than the general population [14].

Participants recruited through clinical settings had a less favourable view of internet interventions compared to the other groups. The recruiters working in these clinical settings viewed internet interventions less favourably than the participants. Understandably, patients engaging with psychiatric or psychotherapeutic treatment and clinical treatment providers may regard internet based treatments with somewhat greater scepticism. Interestingly, recruiters for our study had a more positive view of internet interventions than psychotherapists recruited through professional associations for psychotherapists who were surveyed in a separate study [28]. This might be due to sampling bias: clinicians who are sceptical of internet interventions are less likely to recruit for a study of such an intervention.

Limitations of the study

In spite of this relatively positive attitude, the 89 recruiters only recruited 105 participants for this trial that were eligible to participate and could thus be randomized. This figure must be interpreted with caution though as we could not link study participants to individual recruiters. Therefore, we do not know whether the recruiters surveyed here actually recruited the participants in this study that self-identified as clinically recruited. Still, these figures do suggest that it is more difficult to recruit for an internet intervention through clinical settings compared to recruitment through the media and the

internet. These recruitment difficulties were not related to characteristics of the internet intervention but rather to more general problems with recruiting for studies in a busy clinical routine.

There are some further limitations to consider when interpreting our results. The most common recruitment source was “other”, and most of these participants learned about our study through news media. The clinical recruitment sources were heterogeneous. Most of the clinical recruiters self-identified as psychotherapists. Our results may therefore have been different if we had recruited in general practice. Also, our sample reported mild to moderate depressive symptoms and it is therefore unclear if our results also extend to people with more severe depressive symptoms or other primary mental health complaints. The inclusion of only mild and moderately depressed subjects might also have limited our ability to detect baseline differences in clinical characteristics.

Furthermore, the absence of a statistically significant interaction in our subgroup analysis does not necessarily mean that the treatment effect applies to all subgroups [17]. Statistical power is considerably lower for interaction analyses compared to the main effect analysis, particularly if the subgroups are not identical in size as in our study [34]. Inspection of Table 4 suggests that a differential treatment effect might have attained statistical significance in an even larger sample. We have previously reported that the internet intervention was less effective for patients with mild to moderate depressive symptoms who received concurrent psychiatric or psychotherapeutic treatment [3]. Internet interventions may therefore confer the greatest benefit for individuals who are not in specialized psychiatric or psychotherapeutic care. However, this difference may also depend on symptom severity, as we have previously observed stronger effects among severely depressed individuals who used an internet intervention and received concurrent antidepressant medication [4].

Conclusion

We conclude that the internet intervention studied here (Deprexis) can be regarded as an effective intervention, also when offered in a clinical setting. However, additional replications with patients recruited from clinical settings would be desirable to establish the robustness of this conclusion. In terms of their clinical and demographic characteristics, participants recruited from treatment settings are very similar to participants recruited via insurance companies, internet forums and the media. From a public health perspective, it appears justified to make this intervention available in clinical treatment settings and beyond. When deployed in clinical settings, evidence-based internet interventions could be added to

the repertoire of existing treatments; when deployed outside of treatment settings, they might offer effective help for underserved people who, for various reasons, do not receive other forms of treatment.

Impact of recruitment source in an RCT of an internet intervention for depression.

Tables and Figures

Table 1: Differences in demographic data between different recruitment sources.

	Recruitment Source											Statistics		
	(1) Clinical			(2) Internet Forums			(3) Insurance			(4) Other		Between groups		
Demographic characteristics	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*df*	*F*	*p*
Age	105	41.58	11.930	171	41.89	11.239	271	43.32	9.777	466	43.23	11.327	3,1009	1.250	.290
Marital Status	*n*	*n*	*%*	*n*	*n*	*%*	*n*	*n*	*%*	*N*	*n*	*%*	*df*	chi^2	*p*
Married and cohabiting		36	34.3%		57	33.3%		131	48.3%		201	43.1%			
Married and not cohabiting		4	3.8%		5	2.9%		9	3.3%		10	2.1%			
Committed relation		24	22.9%		32	18.7%		44	16.2%		89	19.1%			
Single	105	29	27.6%	171	51	29.8%	271	51	18.8%	466	116	24.9%	15	30.29	.011
Divorced		10	9.5%		21	12.3%		35	12.9%		49	10.5%			
Widowed		2	1.9%		5	2.9%		1	0.4%		1	0.2%			
Education status	*n*	*n*	*%*	*n*	*n*	*%*	*n*	*n*	*%*	*n*	*n*	*%*	*df*	chi^2	*p*
Highest secondary		52	49.5%		87	50.9%		118	43.5%		263	56.4%			
Higher secondary		15	14.3%		38	22.2%		54	19.9%		65	13.9%			
Middle secondary		27	25.7%		35	20.5%		84	31.0%		97	20.8%			
Lower secondary	105	6	5.7%	171	8	4.7%	271	12	4.4%	466	27	5.8%	18	37.21	.005
Still in school		1	1.0%		0	0%		0	0%		1	0.2%			
No degree		1	1.0%		0	0%		0	0%		0	0%			
Other		3	2.9%		3	1.8%		3	1.1%		13	2.8%			
Employment status	*n*	*n*	*%*	*n*	*n*	*%*	*n*	*n*	*%*	*n*	*n*	*%*	*df*	chi^2	*p*
Full-time		44	41.9%		65	38.0%		136	50.2%		189	40.6%			
Part time	105	17	16.2%	171	32	18.7%	271	75	27.7%	466	103	22.1%	9	30.24	< .001
Other		18	17.1%		27	15.8%		24	8.9%		62	13.3%			
None		26	24.8%		47	27.5%		36	13.3%		112	24.0%			

Impact of recruitment source in an RCT of an internet intervention for depression.

Table 2: Differences in clinical characteristics between different recruitment sources.

FEP-2: broad self-rated symptom measure covering dimensions ranging from general well-being to interpersonal relationships, HRSD: clinician-rated depression severity, PHQ-9: self-rated depression severity, SF-12 PH: physical health related quality of life, SF-12 MH: mental health related quality of life, WSQ: web screening questionnaire for mental disorders.

	Recruitment Source											Statistics		
	(1) Clinical			(2) Internet Forum			(3) Insurance			(4) Other		Between groups		
Clinical characteristics	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*df*	*F*	*p*
PHQ-9	105	10.06	2.60	171	10.21	2.44	271	10.40	2.39	466	10.30	2.38	3,1009	0.57	.635
PHQ-9 suicidality item		1.30	0.48		1.23	0.45		1.21	0.41		1.27	0.46		1.91	.127
SF-12 PH	102	46.42	9.52	169	46.83	9.91	262	47.64	9.06	456	48.05	9.44	3,985	1.25	.291
SF-12 MH		30.11	6.96		31.39	8.45		31.49	7.34		31.51	7.69		0.99	.398
FEP-2	105	2.93	0.47	171	2.99	0.47	271	2.92	0.46	466	2.918	0.45	3,1009	1.08	.357
HRSD		17.47	7.49		17.49	7.58		16.14	7.47		16.73	7.41		1.48	.219
Diagnosis	*n*	*n*	*%*	*n*	*n*	*%*	*n*	*N*	*%*	*n*	*n*	*%*	*df*	*chi²*	*p*
Dysthymia		33	31.4%		77	45.0%		100	36.9%		166	35.6%		6.49	.090
Depressive Episode		36	34.3%		47	27.5%		75	27.7%		132	28.3%		1.90	.594
More than 5 episodes	105	36	34.3%	171	66	38.6%	271	99	36.5%	466	192	41.2%	3	2.62	.453
Panic d/o (WSQ)		40	38.1%		47	27.5%		75	27.7%		159	34.1%		6.68	.083
Social phobia (WSQ)		46	43.8%		80	46.8%		127	46.9%		221	47.4%		0.45	.930
Alcohol use d/o (WSQ)		4	3.8%		6	3.5%		11	4.1%		31	6.7%		4.16	.245
Resource use	*n*	*n*	*%*	*n*	*n*	*%*	*n*	*n*	*%*	*n*	*n*	*%*	*df*	*chi²*	*p*
General practitioner		92	87.6%		141	82.5%		240	88.6%		397	85.2%		3.70	.295
Psychiatrist		44	41.9%		72	42.1%		57	21.0%		139	29.8%		28.67	< .001
Psychotherapist		52	49.5%		73	42.7%		73	26.9%		155	33.3%	3	22.58	< .001
Neurologist	105	20	19.0%	171	38	22.2%	271	39	14.4%	466	62	13.3%		8.76	.033
Inpatient psychiatry		19	18.1%		15	8.8%		14	5.2%		29	6.2%		20.35	< .001
		M	*SD*		*M*	*SD*		*M*	*SD*		*M*	*SD*	*df*	*F*	*p*
Sick leave days		40.13	66.68		29.99	53.54		15.72	36.41		20.15	43.40	3,1009	8.81	< .001

Impact of recruitment source in an RCT of an internet intervention for depression.

Table 3: Differences in attitude to psychological internet intervention.

	Recruitment Source												Statistics		
	(1) Clinical			(2) Internet Forum			(3) Insurance			(4) Other			Between groups		
APOI score	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*df*	*F*	*p*
Scepticism and Risk Perception	105	9.86	2.38	169	9.88	2.25	270	9.36	2.28	460	9.30	2.31	3,1009	3.86	0.009
Confidence in Effectiveness		16.43	2.15		16.44	2.14		16.66	2.03		16.74	2.15		1.19	0.314
Technologization Threat		12.47	2.12		12.04	2.50		11.52	2.41		11.63	2.53		4.91	0.002
Anonymity Benefits		11.48	2.88		12.62	2.61		12.70	3.07		12.47	3.19		4.37	0.005
Total		53.58	6.37		55.14	6.72		56.47	6.83		56.28	6.96		5.85	0.001

Impact of recruitment source in an RCT of an internet intervention for depression.

Table 4: Main effect of treatment and treatment by recruitment source interaction on estimated mean change in self-rated depressive symptoms (PHQ-9) from baseline to post and follow-up and minimally clinically relevant change of PHQ-9 at post assessment.

The sum of participants in the treatment groups (intervention plus CAU) is smaller than the number of participants in each subgroup because some participants did not complete the post or the follow-up assessment and could therefore not be included in the main analysis. A sensitivity analysis using multiple imputation to replace missing values yielded essentially the same results as the main analysis.

Recruitment source	Treatment	Estimated change				Effect Size		Minimally clinically important change of PHQ-9		Effect size	
		M	*SE*	*95% CI*		*d*	*95% CI*	*n*	*%*	*NNT*	*95% CI*
Main effect of treatment		$F_{1,823}$ = 21.84, *p* < .001						*B* = 1.18 (*SE* .51), *p* = .021			
All (n = 1013)	Intervention (n = 509)	2.94	.21	2.53	3.35	0.30	0.01 – 0.59	143	28.1	9	6 – 15
	CAU (n = 504)	1.51	.21	1.09	1.92			83	16.5		
Treatment by recruitment source interaction		$F_{3,817}$=0.29, *p* = .83						*B* = -0.16 (*SE* .16), *p* = .31			
Clinical (n = 105)	Intervention (n = 42)	3.30	.54	2.24	4.37	0.27	-0.49 – 1.04	17	29.8	5	-3 – 107
	CAU (n = 38)	2.35	.58	1.21	2.49			8	16.7		
Internet forums (n = 171)	Intervention (n = 63)	2.20	.46	1.30	3.10	0.39	-0.23 – 1.01	23	28.0	5	3 – 15
	CAU (n = 62)	0.81	.45	-0.07	1.69			9	10.1		
Insurance (n = 271)	Intervention (n = 106)	3.24	.35	2.56	3.93	0.48	0.00 – 0.96	40	29.9	7	4 – 39
	CAU (n = 113)	1.52	.34	0.85	2.19			26	19.0		
Other (n = 466)	Intervention (n = 184)	3.00	.27	2.48	3.52	0.46	0.09 – 0.83	63	26.7	8	5 – 28
	CAU (n = 186)	1.34	.27	0.81	1.87			40	17.4		

Impact of recruitment source in an RCT of an internet intervention for depression.

Table 5: Main effect of treatment, main effect of recruitment source and treatment by recruitment source interaction on estimated mean change in secondary outcomes.

FEP-2: broad self-rated symptom measure covering dimensions ranging from general well-being to interpersonal relationships, HRSD: clinician-rated depression severity, SF-12 PH: physical health related quality of life, SF-12 MH: mental health related quality of life.

	Main effect of treatment			Main effect of recruitment source			Treatment by recruitment source interaction		
	df	*F*	*p*	*df*	*F*	*p*	*df*	*F*	*p*
HRSD	1,696	11.82	.001	3,688	1.26	.300	3,687	32.99	.551
FEP-2	1,819	76.17	< .001	3,815	2.40	.067	3,814	0.141	.935
SF-12 PH	1,789	2.23	.135	3,785	0.312	.816	3,784	0.319	.811
SF-12 MH	1,789	136.06	< .001	3,785	3.736	.011	3,784	0.972	.405

Impact of recruitment source in an RCT of an internet intervention for depression.

Disclosures

Competing interests

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 and Hogrefe) on psychotherapy for chronic depression and on psychiatric emergencies. BM is employed as research director at GAIA AG, the company that developed, owns, and operates the internet intervention “Deprexis”. MH is a consultant of Servier. He was an invited speaker at several workshops and continuous education workshops over the last two years. All the other authors report no relationships with commercial interests.

Contributors

The principal investigators (TB, FH, JPK, BM and SM) designed the study and obtained funding. The EVIDENT study steering committee (TB, JPK, BM, SM, CS, and JS) further developed the study design in collaboration with the EVIDENT study group (steering committee and Wolfgang Greiner, Bielefeld; MH; WL; Matthias Rose, Berlin) and CG. Patient recruitment was coordinated by the EVIDENT study group. JPK conducted the statistical analyses with substantial input from EV. The results were interpreted by the steering committee with substantial input from the study group and CG. JPK wrote the manuscript with substantial input from the steering committee and CG. All authors commented on the manuscript and approved the final version.

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Data sharing statement

No additional data are available.

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Section/Topic	Item No	Checklist item	Reported on page No
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	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	7
	2b	Specific objectives or hypotheses	8
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n.a.
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n.a.
Sample size	7a	How sample size was determined	10 / 15
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n.a.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Available in main publication
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Available in main publication
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	9
	11b	If relevant, description of the similarity of interventions	n.a.
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup	10

		analyses and adjusted analyses	
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	13b	For each group, losses and exclusions after randomisation, together with reasons	11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Available in main publication
	14b	Why the trial ended or was stopped	n.a.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	17
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	20
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	20
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Protocol	24	Where the full trial protocol can be accessed, if available	8
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	5

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Does recruitment source moderate treatment effectiveness? A subgroup analysis from the EVIDENT study, a randomised controlled trial of an internet intervention for depressive symptoms.

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Impact of recruitment source in an RCT of an internet intervention for depression.

Cover Pages

Title

Does recruitment source moderate treatment effectiveness? A subgroup analysis from the EVIDENT study, a randomised controlled trial of an internet intervention for depressive symptoms.

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Impact of recruitment source in an RCT of an internet intervention for depression.

Key words: internet intervention; cognitive behaviour therapy; depression; randomized controlled trial; recruitment source.

Impact of recruitment source in an RCT of an internet intervention for depression.

Abstract

Objective: Examine whether the effects of internet interventions for depression generalize to participants recruited in clinical settings.

Design: subgroup analysis of the results of a randomized, controlled, single-blind trial.

Setting: five diagnostic centers in Germany.

Participants: 1,013 people with mild to moderate depressive symptoms were recruited from clinical sources as well as internet forums, statuatory insurance companies, and other sources.

Interventions: either care-as-usual alone (control) or a 12-week internet intervention (Deprexis) plus usual care (intervention).

Main outcome measures: The primary outcome measure was self-rated depression severity (Patient Health Questionnaire: PHQ-9). Further measures ranged from demographic and clinical parameters to a measure of attitutes towards internet interventions (APOI).

Results: The recruitment source was only associated with very few of the examined demographic and clinical characteristics. Compared to participants recruited from clinical sources, participants recruited through insurance companies were more likely to be employed. Clinically recruited participants were as severely affected as those from other recruitment sources but more skeptical of internet interventions. The effectiveness of the intervention was not differentially associated with recruitment source (treatment by recruitment source interaction $F_{3,824} = 0.28$, $p = .84$).

Conclusion: Our results support the hypothesis that the intervention we studied is effective across different recruitment sources including clinical settings.

Trial registration number: ClinicalTrials.gov NCT01636752.

Impact of recruitment source in an RCT of an internet intervention for depression.

Strengths and limitations of this study

- Ours is the first trial to examine the effect of recruitment source on outcome.
- The large sample size makes detection of subgroup effects more likely.
- The absence of a subgroup effect does not prove that the effect applies to all subgroups.
- More randomized trials of internet interventions in clinical settings are needed.

Impact of recruitment source in an RCT of an internet intervention for depression.

Background

Numerous studies [1-4] and meta-analyses [5-10] have shown that internet interventions are effective in the treatment of a broad array of psychiatric disorders, ranging from depression [5-7] and anxiety [7-9] to posttraumatic stress disorder [10] and schizophrenia [1,2]. However, most participants in these studies have been recruited through media advertisements [7,9], so it remains unclear whether they are similar to those seeking face-to-face treatment in regular clinical settings [7] and whether the effects for internet interventions generalize across different recruitment settings [5].

Although some studies suggest that the promising results from efficacy studies can be transferred to routine clinical practice [11,12], one recent study [13] of two internet interventions in primary care reported null findings. This is not necessarily due to the fact that these interventions are not effective in primary care but might be explained by insufficient use of the interventions. No previous studies have directly examined whether differences in recruitment source are associated with the effectiveness of depression-focused internet interventions.

A better understanding of whether participants recruited from different sources differ in other important characteristics could help investigators avoid sampling bias or target specific clinical or demographic subgroups. Previous studies have addressed associations of recruitment source with patient characteristics in an internet clinic [14], in a trial of an internet intervention [15] and in a trial of face-to-face psychotherapy for depression [16]. It might also be important to know if participants from certain recruitment sources are particularly open-minded towards internet interventions. But none of the previous studies have compared attitudes towards internet interventions across different recruitment sources.

Subgroup analyses examining associations between recruitment source and intervention effectiveness require large sample sizes [17]. We have recently published one of the largest randomized trials of an internet intervention, the EVIDENT trial [3]. Over one thousand participants were randomized for this trial that demonstrated the effectiveness of the intervention (Deprexis) for mild to moderate depressive symptoms. In the EVIDENT trial, we also developed a novel questionnaire measuring positive and negative attitudes towards internet interventions [18].

Using the EVIDENT trial data set, the current paper has two main objectives: firstly, we sought to examine whether recruitment source is systematically associated with various baseline parameters,

including demographic and clinical characteristics as well as attitudes towards internet interventions. Secondly, we aimed to examine whether recruitment source is differentially associated with the effectiveness of the intervention. We also report on our general experiences with regard to recruiting participants from clinical settings in the EVIDENT trial.

Methods

The EVIDENT study is a multicentre (diagnostic interviews were conducted in five sites in Germany), randomized controlled trial (RCT). The trial was approved by the Ethics Committee of the German Psychological Association (DGPs SM 04_2012) and is registered with ClinicalTrials.gov (NCT01636752). The full study protocol has been published [19].

Participants

Participants were recruited via multiple settings and online informed consent was obtained prior to the baseline assessment. The main recruitment sources were internet forums for depression, magazines for members of statutory German health insurance companies and various inpatient and outpatient clinics, ranging from general practitioners' practices to psychiatrists' and psychotherapists' clinics, practices, and hospital settings.

Recruitment source was assessed by self-report; specifically, a combination of a multiple-choice question (clinical setting, internet forums, insurance company, other) and a free-text answer was used to identify the exact source via which each patient was recruited. One of the authors (CG) cross-checked the free-text answers against the multiple-choice answer and resolved any discrepancies through discussion with her local study team (CS and JPK).

The main inclusion criterion for the RCT was the presence of self-reported mild to moderate depressive symptoms, operationalized as a score from 5 to 14 on the Patient Health Questionnaire-9 (PHQ-9) [20]. Eligible participants were from 18 to 65 years of age, had internet access and were able to communicate in German. Participants with acute suicidality or a lifetime diagnosis of bipolar disorder or schizophrenia were excluded.

Interventions

Following a naturalistic and pragmatic design approach, care-as-usual was not influenced by the investigators. All participants were permitted to use any form of treatment, including antidepressant

medication and psychotherapy. Participants were randomized equally (1:1) to the two groups (intervention or control). Participants in the control condition received only care-as-usual (hereafter referred to as the CAU group). They were offered access to the internet intervention after the last follow-up assessment. Participants in the intervention group received immediate access to the internet intervention (Deprexis) in addition to care-as-usual. Briefly, this program consists of modules covering content that is broadly consistent with CBT (e.g., cognitive restructuring, behavioural activation, acceptance and mindfulness, problem-solving) [21]. The intervention can be used with or without guidance by a clinician [22]. In our trial, participants randomized to the intervention group with an initial PHQ-9 score from 10 to 14 received the guided version (e-mail support); those scoring from 5 to 9 on the PHQ-9 received the unguided version.

Outcome measures

The primary outcome for the RCT was change on the *Patient Health Questionnaire (PHQ-9)* [20]. The internal consistency of the PHQ-9 based on the trial data was good (Cronbach's alpha = 0.83). The *Mini International Neuropsychiatric Interview (MINI)* [23] was used to assess the presence of a depressive disorder as well as to rule out a lifetime diagnosis of bipolar disorder or schizophrenia. Clinician-rated severity of depression was assessed with the 24-item version of the *Hamilton Depression Rating Scale* [24] (Cronbach's alpha = 0.79). The MINI and the HDRS-24 were administered via telephone by trained raters.

Attitudes towards internet interventions were assessed using a questionnaire that was developed during this trial, the *Attitudes towards Psychological Online Interventions Questionnaire (APOI)* [18]. The APOI is the first questionnaire that measures both positive and negative attitudes towards internet interventions in general. It comprises four subscales with scores ranging from 4 to 20, and these are labelled "scepticism and perception of risks", "confidence in effectiveness", "technologization threat" and "anonymity benefits". The total score ranges from 16 to 80 with higher scores reflecting a more favourable attitude towards internet interventions. When calculating the total score, the polarity of the subscale scores for "scepticism and perception of risks" and "technologization threat" is reversed so that all subscales contribute equally to the total score. The internal consistency of the APOI in this sample is acceptable to good (Cronbach's alpha = 0.77).

Demographic details and treatment history were assessed with non-standardized questionnaires. We also employed the following self-rating scales: a measure of health-related quality of life (*Short-Form*

Health Survey: SF-12) [25] that covers physical health related qualitiy of life (SF-12 PH) and mental health related quality of life (SF-12 MH); a broad symptom measure covering dimensions ranging from general well-being to interpersonal relationships (*Questionnaire for the Evaluation of Psychotherapeutic Processes - FEP-2)* [26] and the *Web Screening Questionnaire (WSQ)*, an instrument screening for frequent mental disorders [27].

Assessments

The PHQ-9 was administered via online questionnaires along with all the other self-ratings at baseline, after three months (post assessment) and after six months (follow-up assessment). Raters contacted participants for the MINI and the HDRS-24 at baseline and after three months.

Recruiter survey

We also invited the clinicians recruiting for our study to participate in an online survey. They were asked to provide demographic data and to complete two questionnaires: an unstandardized questionnaire that assessed their recruitment experience and the *Attitudes towards Psychological Online Interventions Questionnaire,* adapted for healthcare professionals *(APOI-HP)* [28].

Statistical analysis

Statistical analyses were performed with SPSS 22 (IBM Corporation). We calculated univariate ANOVAs for continuous variables. Post-hoc tests were Bonferroni-corrected for multiple comparisons. For categorical variables, we calculated univariate multinomial logistic regression analyses. Effect sizes are presented as Cohen's d for continuous data and numbers needed to treat (NNT) for dichotomous data.

For the analysis of the effect of the recruitment source on treatment effectiveness, we used linear mixed models (LMM), as they have the advantage of using all available data of each subject. They also offer the opportunity to choose an appropriate covariance structure reflecting the potential dependence due to repeated measurements [29]. Adjustment for baseline measure was chosen as this accounts for regression to the mean [30]. The analysis followed the intention-to-treat principle, which included all randomized participants. No missing values were substituted as LMMs based on all observed data are valid and unbiased methods for missing at random (MAR) data [31].

The outcome was analysed as change from baseline with a random intercept for the participant. Time, treatment group, recruitment source and the interaction term treatment by recruitment source were

entered as fixed effects. We chose an autoregressive covariance structure and allowed variances to vary between assessment points. The choice was based on Akaike's Information Criterion (AIC) from a fixed set of candidate structures, namely a first order autoregressive (AR1), or scaled identity structure or heterogeneous versions thereof. The hypothesis that the recruitment source influences the effect of the intervention on depressive symptoms was tested on the treatment by recruitment source interaction. Here, the effect of the intervention is defined as the mean difference between average change in outcome for the intervention group minus average change in outcome for the CAU group (the difference in differences). The subgroup analysis had been pre-specified in the study protocol [19].

Results

Recruitment and participant flow

For the participant flow chart please refer to the report of the main results of this study [19]. Briefly, 2020 participants were assessed for eligibilty, and 1007 (49.9%) were excluded. The most common exclusion criterion was exceeding a score of 14 on the PHQ-9 (748, 37.0%). Non-completion rates for the main outcome measure were 21.6% at post assessment (*n* = 219) and 24.6% at follow-up (*n* = 259). The non-completion rate did not differ between the different recruitment sources (chi^2_3= 4.34, p = .227 for the post assessment and chi^2_3= 2.06, p = .559 for the follow-up assessment).

Most participants (46%) self-identified as coming from the “other” recruitment source (see Table 1). The remaining participants came from statutory health insurance companies (27%), internet forums (17%) and clinical sources (10%). Inspection of the free-text answers revealed that most of the participants in the “other” category learned about the study through articles in the news media.

Participant characteristics

For descriptive and inferential statistics on the differences between the four recruitment sources, refer to Table 1 (demographic data) and Table 2 (clinical characteristics). Briefly, we did not find any statistically significant differences for a broad range of clinical characteristics including self- and clinician rated depression severity, psychosocial functioning and self-reported comorbid symptoms. Participants recruited through online forums were slightly more likely to suffer from dysthymia and participants from clinical settings and other sources were slightly more likely to report symptoms of panic disorder, but these differences were not statistically significant. We did find statistically significant differences between the recruitment sources for measures of resource use. Compared to participants recruited

through insurance companies and other sources, participants recruited in clinical settings were more likely to be in psychiatric treatment ($p < .05$; odds ratio [OR] vs. insurance 2.71, OR vs. other sources 1.70), psychotherapy ($p < .01$; OR vs. insurance 2.66, OR vs. other sources 1.99) and inpatient psychiatric treatment ($p < .001$; OR vs. insurance 4.06, OR vs. other sources 3.33, OR vs. internet forums 2.30). They also reported having had significantly more sick leave days ($p < .001$; d vs. insurance 0.52, d vs. other sources 0.41).

We also observed differences for demographic variables. Compared to participants recruited in a clinical setting, participants recruited through statutory health insurance companies were more likely to be employed full-time ($p < .01$; OR 2.23) or part-time ($p < .01$; OR 3.19). Participants from the different recruitment sources also differed in their attitudes to internet interventions (Table 3). Compared to participants recruited through insurance companies and other sources, those recruited in clinical settings had less favourable attitudes towards internet interventions ($p < .01$; d vs. insurance 0.43, d vs. other sources 0.40). In particular, they scored higher on technologization threat ($p < .01$; d vs. insurance companies 0.41, d vs. other sources 0.34) and lower on anonymity benefits ($p < .01$; d vs. internet forums 0.42, d vs. insurance companies 0.41, d vs. other sources 0.32).

Intervention usage and utilization of other treatments

A total of 509 participants were randomised to the intervention group. The mean number of sessions of at least 10 minutes duration was 8.32 (*SD* = 4.71), the mean total usage time was 429.70 (*SD* = 294.0) minutes (about seven hours). Periods of inactivity of 5 min or longer were subtracted in the computation of the total usage time. Participants from the different recruitment sources did not differ with respect to the number of sessions ($F_{3,481} = 0.47$, $p = .70$) or the total usage time ($F_{3,481} = 0.51$, $p = .70$). The intervention and the CAU group did not differ with respect to the use of concomitant treatments (e.g. psychotherapy, psychotropic medication) during the study period (Supplemental Table 1).

Primary and secondary outcomes

As reported previously [3], the intervention had a significant effect on the main outcome, change in PHQ-9 scores from baseline to post and follow-up. Whereas depressive symptoms decreased in both groups, changes in PHQ-9 differed significantly (main effect of treatment: $F_{1,829} = 23.05$, $p < .001$) between groups. In the intervention group, PHQ-9 scores decreased by 1.43 (95% CI 0.85 — 2.02) points more than in the CAU group, on average. Both the main effect of recruitment source ($F_{3,825} = 2.61$, $p =$

.051) and the interaction term (treatment assignment by recruitment source) were not statistically significant ($F_{3,824}$ = 0.28, p = .84)(Table 4).

The analysis of the secondary outcomes (HRSD, SF-12 and FEP-2) mostly yielded the same pattern of results (Table 5). The main effect of group was statistically significant for all secondary outcomes except for physicial health-related qualtiy of life (SF-12 PH). The main effect of recruitment source was significant for mental health related quality of life (p = .011) with patients recruited via internet forums reporting smaller improvements compared to participants recruited from clinical settings (-3.82; 95%, CI -7.18 — -0.47; Bonferroni corrected p = .016) and participants recruited from other sources (-2.57; 95%, CI -4.99 — -0.15; Bonferroni corrected p = .030). The interaction term (treatment assignment by recruitment source) was not statistically significant for any of the secondary outcomes.

Sensitivity analyses

As a sensitivity analysis for the primary outcome, we reran the analysis of the interaction with a binary subgroup definition. Here we summarized the following recruitment sources as non-clinical: statutory health insurance companies, internet forums and “other” recruitment sources. Here, we replicated the significant main effect of treatment ($F_{1,834}$ = 7.94, p < .01) and found a significant main effect of recruitment source on change of PHQ-9 ($F_{1,834}$ = 5.45, p = .02). Symptom change was greater in those recruited from clinical sources compared to those not recruited from clinical sources (1.50; 95%, 0.33 — 2.68). The interaction term (treatment by binary recruitment source) was not statistically significant ($F_{1,834}$= 1.66, p = .20) confirming the result of the main subgroup analysis above.

We also conducted a sensitivity analysis with the binary outcome “minimally clinically important change of PHQ-9” as the dependent variable (binary logistic regression: chi^2_3 = 19.749, p < .001, Nagelkerkes r^2 = .031). A minimally clinically important individual PHQ-9 improvement was defined as five point reduction [32]. In keeping with the results of the previously reported analyses we found a main effect of treatment (B = 1.18 (SE .51), p = .021), no main effect of recruitment source (B = 0.08 (SE .13), p = 0.53) and the treatment by recruitment source interaction term was not statistically significant (B = -0.16 (SE .16), p = .31).

Rerunning the primary analysis without baseline correction did not alter our results substantially (main effect of group: $F_{1,827}$ = 20.47, p < .001; main effect of recruitment source on PHQ change: $F_{3,827}$ = 2.28, p = .078; treatment assignment by recruitment source interaction: $F_{3,827}$ = 0.18, p = .91). In a final sensitivity

analysis we used multiple imputation (50 imputations) to estimate missing scores by evaluating the relationships between observed and missing scores as well as baseline scores. The results were essentially the same as for the main analysis (main effect of treatment: $F_{1,1004}$ = 111.52, p < .001; main effect of recruitment source on change of PHQ-9: $F_{3,1004}$ = 2.547, p = .055; treatment assignment by recruitment source interaction: $F_{3,1004}$ = 0.45, p = .72).

Recruiter characteristics

A total of 89 persons who supported our recruitment efforts in clinical settings (the recruiters) were contacted via e-mail for an online survey. Of these, 48 completed the survey (54%). They were mostly female (69%) and their mean age was 44.06 (SD 12.17). Almost half of them reported working in an inpatient setting (42%), mostly as psychotherapists (50%), specialists in psychosomatic medicine (33%) and psychiatry (22.9%). Recruiters could name multiple fields of work and, therefore, the total sum exceeds 100%. Recruiters also completed a questionnaire inquiring about their experiences with regard to the recruitment process. Here, 40% reported that they often forgot to talk with their patients about the study. 25% wrote they did not have the time to talk with their patients about the study or that their patients' symptoms were too severe to participate in the study. Only 12.5% of respondents reported inadequate computer literacy as a barrier to participating in the study. On the APOI, the recruiters had a total mean score of 51.23 (SD 12.17) and the following subscale mean scores (SD): scepticism and risk perception 11.14 (2.55), confidence in effectiveness 16.08 (1.92) perceived technology disadvantages 14.50 (SD 2.34) and perception of anonymity benefits 12.64 (2.47).

Discussion

Principal findings

This study examined associations of recruitment source with participant characteristics and effectiveness in a trial of an internet intervention for depressive symptoms. We found few demographic or clinical differences among participants recruited from different sources. To our knowledge, this is the first study that examines the association of the recruitment source with the effectiveness of an internet intervention. Here, we found no moderating influence of the recruitment source on the treatment effect. We did find an indication however that the recruitment source might predict course of depressive symptoms independent of treatment group assignment. Decrease of symptoms was greater in those recruited from clinical sources than in those recruited via other settings. This finding was only statistically

significant in one of the sensitivity analysis though and should thus be replicated in other studies before firm conclusions can be drawn from this finding.

Comparison with other studies

Some of the findings regarding clinical characteristics contrast with results from a previous study [15], which found somewhat more severe symptoms in patients recruited through clinical settings. Participants recruited in clinical settings in our study were more likely to be on sick-leave, suggesting that despite similar current symptom severity, their symptom-related psychosocial impairment in the six months preceding randomization might have been greater. Even though participants recruited in clinical settings did not differ from others in depression severity or quality of life, they were about twice as likely to be in psychiatric treatment, compared to participants recruited via health insurance companies (OR 2.71) or other sources, such as news media (OR 1.70). This might indicate that internet interventions reach people who chose not to seek treatment through more conventional means in spite of substantial symptom severity [33].

We have found that participants recruited through insurance companies were more likely to be employed. Also we observed a significant between groups difference regarding level of education. These findings might provide some orientation for researchers wishing to recruit participants with certain demographics as it has been noted that participants in internet studies as well as outpatient treatment centres are more highly educated than the general population [14].

Participants recruited through clinical settings had a less favourable view of internet interventions compared to the other groups. The recruiters working in these clinical settings viewed internet interventions less favourably than the participants. Understandably, patients engaging with psychiatric or psychotherapeutic treatment and clinical treatment providers may regard internet based treatments with somewhat greater scepticism. Interestingly, recruiters for our study had a more positive view of internet interventions than psychotherapists recruited through professional associations for psychotherapists who were surveyed in a separate study [28]. This might be due to sampling bias: clinicians who are sceptical of internet interventions are less likely to recruit for a study of such an intervention.

Limitations of the study

In spite of this relatively positive attitude, the 89 recruiters only recruited 105 participants for this trial that were eligible to participate and could thus be randomized. This figure must be interpreted with caution though as we could not link study participants to individual recruiters. Therefore, we do not know whether the recruiters surveyed here actually recruited the participants in this study that self-identified as clinically recruited. Still, these figures do suggest that it is more difficult to recruit for an internet intervention through clinical settings compared to recruitment through the media and the internet. These recruitment difficulties were not related to characteristics of the internet intervention but rather to more general problems with recruiting for studies in a busy clinical routine.

There are some further limitations to consider when interpreting our results. The most common recruitment source was “other”, and most of these participants learned about our study through news media. The clinical recruitment sources were heterogeneous. Most of the clinical recruiters self-identified as psychotherapists. Our results may therefore have been different if we had recruited in general practice. Also, our sample reported mild to moderate depressive symptoms and it is therefore unclear if our results also extend to people with more severe depressive symptoms or other primary mental health complaints. The inclusion of only mild and moderately depressed subjects might also have limited our ability to detect baseline differences in clinical characteristics.

Furthermore, the absence of a statistically significant interaction in our subgroup analysis does not necessarily mean that the treatment effect applies to all subgroups [17]. Statistical power is considerably lower for interaction analyses compared to the main effect analysis, particularly if the subgroups are not identical in size as in our study [34]. Inspection of Table 4 suggests that a differential treatment effect might have attained statistical significance in an even larger sample. We have previously reported that the internet intervention was less effective for patients with mild to moderate depressive symptoms who received concurrent psychiatric or psychotherapeutic treatment [3]. Internet interventions may therefore confer the greatest benefit for individuals who are not in specialized psychiatric or psychotherapeutic care. However, this difference may also depend on symptom severity, as we have previously observed stronger effects among severely depressed individuals who used an internet intervention and received concurrent antidepressant medication [4].

Impact of recruitment source in an RCT of an internet intervention for depression.

Conclusion

We conclude that the internet intervention studied here can be regarded as an effective intervention, also when offered in a clinical setting. However, additional replications with patients recruited from clinical settings would be desirable to establish the robustness of this conclusion. In terms of their clinical and demographic characteristics, participants recruited from treatment settings are very similar to participants recruited via insurance companies, internet forums and the media. From a public health perspective, it appears justified to make this intervention available in clinical treatment settings and beyond. When deployed in clinical settings, evidence-based internet interventions could be added to the repertoire of existing treatments; when deployed outside of treatment settings, they might offer effective help for underserved people who, for various reasons, do not receive other forms of treatment.

Impact of recruitment source in an RCT of an internet intervention for depression.

Tables and Figures

Table 1: Differences in demographic data between different recruitment sources.

	Recruitment Source											Statistics		
	(1) Clinical			(2) Internet Forums			(3) Insurance			(4) Other			Between groups		
Demographic characteristics	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*df*	*F*	*p*
Age	105	41.58	11.930	171	41.89	11.239	271	43.32	9.777	466	43.23	11.327	3,1009	1.250	.290
Marital Status	*n*	*n*	*%*	*n*	*n*	*%*	*n*	*n*	*%*	*N*	*n*	*%*	*df*	*chi²*	*p*
Married and cohabiting		36	34.3%		57	33.3%		131	48.3%		201	43.1%			
Married and not cohabiting		4	3.8%		5	2.9%		9	3.3%		10	2.1%			
Committed relation	105	24	22.9%	171	32	18.7%	271	44	16.2%	466	89	19.1%	15	30.29	.011
Single		29	27.6%		51	29.8%		51	18.8%		116	24.9%			
Divorced		10	9.5%		21	12.3%		35	12.9%		49	10.5%			
Widowed		2	1.9%		5	2.9%		1	0.4%		1	0.2%			
Education status	*n*	*n*	*%*	*n*	*n*	*%*	*n*	*n*	*%*	*n*	*n*	*%*	*df*	*chi²*	*p*
Highest secondary		52	49.5%		87	50.9%		118	43.5%		263	56.4%			
Higher secondary		15	14.3%		38	22.2%		54	19.9%		65	13.9%			
Middle secondary		27	25.7%		35	20.5%		84	31.0%		97	20.8%			
Lower secondary	105	6	5.7%	171	8	4.7%	271	12	4.4%	466	27	5.8%	18	37.21	.005
Still in school		1	1.0%		0	0%		0	0%		1	0.2%			
No degree		1	1.0%		0	0%		0	0%		0	0%			
Other		3	2.9%		3	1.8%		3	1.1%		13	2.8%			
Employment status	*n*	*n*	*%*	*n*	*n*	*%*	*n*	*n*	*%*	*n*	*n*	*%*	*df*	*chi²*	*p*
Full-time		44	41.9%		65	38.0%		136	50.2%		189	40.6%			
Part time	105	17	16.2%	171	32	18.7%	271	75	27.7%	466	103	22.1%	9	30.24	< .001
Other		18	17.1%		27	15.8%		24	8.9%		62	13.3%			
None		26	24.8%		47	27.5%		36	13.3%		112	24.0%			

Impact of recruitment source in an RCT of an internet intervention for depression.

Table 2: Differences in clinical characteristics between different recruitment sources.

FEP-2: broad self-rated symptom measure covering dimensions ranging from general well-being to interpersonal relationships, HRSD: clinician-rated depression severity, PHQ-9: self-rated depression severity, SF-12 PH: physical health related quality of life, SF-12 MH: mental health related quality of life, WSQ: web screening questionnaire for mental disorders.

	Recruitment Source											Statistics		
	(1) Clinical			(2) Internet Forum			(3) Insurance			(4) Other		Between groups		
Clinical characteristics	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*df*	*F*	*p*
PHQ-9	105	10.06	2.60	171	10.21	2.44	271	10.40	2.39	466	10.30	2.38	3,1009	0.57	.635
PHQ-9 suicidality item		1.30	0.48		1.23	0.45		1.21	0.41		1.27	0.46		1.91	.127
SF-12 PH	102	46.42	9.52	169	46.83	9.91	262	47.64	9.06	456	48.05	9.44	3,985	1.25	.291
SF-12 MH		30.11	6.96		31.39	8.45		31.49	7.34		31.51	7.69		0.99	.398
FEP-2	105	2.93	0.47	171	2.99	0.47	271	2.92	0.46	466	2.918	0.45	3,1009	1.08	.357
HRSD		17.47	7.49		17.49	7.58		16.14	7.47		16.73	7.41		1.48	.219
Diagnosis	*n*	*n*	*%*	*n*	*n*	*%*	*n*	*N*	*%*	*n*	*n*	*%*	*df*	*chi²*	*p*
Dysthymia		33	31.4%		77	45.0%		100	36.9%		166	35.6%		6.49	.090
Depressive Episode		36	34.3%		47	27.5%		75	27.7%		132	28.3%		1.90	.594
More than 5 episodes	105	36	34.3%	171	66	38.6%	271	99	36.5%	466	192	41.2%	3	2.62	.453
Panic d/o (WSQ)		40	38.1%		47	27.5%		75	27.7%		159	34.1%		6.68	.083
Social phobia (WSQ)		46	43.8%		80	46.8%		127	46.9%		221	47.4%		0.45	.930
Alcohol use d/o (WSQ)		4	3.8%		6	3.5%		11	4.1%		31	6.7%		4.16	.245
Resource use	*n*	*n*	*%*	*n*	*n*	*%*	*n*	*n*	*%*	*n*	*n*	*%*	*df*	*chi²*	*p*
General practitioner		92	87.6%		141	82.5%		240	88.6%		397	85.2%		3.70	.295
Psychiatrist		44	41.9%		72	42.1%		57	21.0%		139	29.8%		28.67	< .001
Psychotherapist		52	49.5%		73	42.7%		73	26.9%		155	33.3%	3	22.58	< .001
Neurologist	105	20	19.0%	171	38	22.2%	271	39	14.4%	466	62	13.3%		8.76	.033
Inpatient psychiatry		19	18.1%		15	8.8%		14	5.2%		29	6.2%		20.35	< .001
		M	*SD*		*M*	*SD*		*M*	*SD*		*M*	*SD*	*df*	*F*	*p*
Sick leave days		40.13	66.68		29.99	53.54		15.72	36.41		20.15	43.40	3,1009	8.81	< .001

Impact of recruitment source in an RCT of an internet intervention for depression.

Table 3: Differences in attitude to psychological internet intervention.

	Recruitment Source												Statistics		
	(1) Clinical			(2) Internet Forum			(3) Insurance			(4) Other			Between groups		
APOI score	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*df*	*F*	*p*
Scepticism and Risk Perception	105	9.86	2.38	169	9.88	2.25	270	9.36	2.28	460	9.30	2.31	3,1009	3.86	0.009
Confidence in Effectiveness		16.43	2.15		16.44	2.14		16.66	2.03		16.74	2.15		1.19	0.314
Technologization Threat		12.47	2.12		12.04	2.50		11.52	2.41		11.63	2.53		4.91	0.002
Anonymity Benefits		11.48	2.88		12.62	2.61		12.70	3.07		12.47	3.19		4.37	0.005
Total		53.58	6.37		55.14	6.72		56.47	6.83		56.28	6.96		5.85	0.001

Impact of recruitment source in an RCT of an internet intervention for depression.

Table 4: Main effect of treatment and treatment by recruitment source interaction on estimated mean change in self-rated depressive symptoms (PHQ-9) from baseline to post and follow-up and minimally clinically relevant change of PHQ-9 at post assessment.

The sum of participants in the treatment groups (intervention plus CAU) is smaller than the number of participants in each subgroup because some participants did not complete the post or the follow-up assessment and could therefore not be included in the main analysis. A sensitivity analysis using multiple imputation to replace missing values yielded essentially the same results as the main analysis.

Recruitment source	Treatment	Estimated change				Effect Size		Minimally clinically important change of PHQ-9		Effect size	
		M	*SE*	*95% CI*		*d*	*95% CI*	*n*	*%*	*NNT*	*95% CI*
Main effect of treatment		$F_{1,823}$ = 21.84, *p* < .001						*B* = 1.18 (*SE* .51), *p* = .021			
All (n = 1013)	Intervention (n = 509)	2.94	.21	2.53	3.35	0.30	0.01 – 0.59	143	28.1	9	6 – 15
	CAU (n = 504)	1.51	.21	1.09	1.92			83	16.5		
Treatment by recruitment source interaction		$F_{3,817}$=0.29, *p* = .83						*B* = -0.16 (*SE* .16), *p* = .31			
Clinical (n = 105)	Intervention (n = 42)	3.30	.54	2.24	4.37	0.27	-0.49 – 1.04	17	29.8	5	-3 – 107
	CAU (n = 38)	2.35	.58	1.21	2.49			8	16.7		
Internet forums (n = 171)	Intervention (n = 63)	2.20	.46	1.30	3.10	0.39	-0.23 – 1.01	23	28.0	5	3 – 15
	CAU (n = 62)	0.81	.45	-0.07	1.69			9	10.1		
Insurance (n = 271)	Intervention (n = 106)	3.24	.35	2.56	3.93	0.48	0.00 – 0.96	40	29.9	7	4 – 39
	CAU (n = 113)	1.52	.34	0.85	2.19			26	19.0		
Other (n = 466)	Intervention (n = 184)	3.00	.27	2.48	3.52	0.46	0.09 – 0.83	63	26.7	8	5 – 28
	CAU (n = 186)	1.34	.27	0.81	1.87			40	17.4		

Impact of recruitment source in an RCT of an internet intervention for depression.

Table 5: Main effect of treatment, main effect of recruitment source and treatment by recruitment source interaction on estimated mean change in secondary outcomes.

FEP-2: broad self-rated symptom measure covering dimensions ranging from general well-being to interpersonal relationships, HRSD: clinician-rated depression severity, SF-12 PH: physical health related quality of life, SF-12 MH: mental health related quality of life.

	Main effect of treatment			Main effect of recruitment source			Treatment by recruitment source interaction		
	df	*F*	*p*	*df*	*F*	*p*	*df*	*F*	*p*
HRSD	1,696	11.82	.001	3,688	1.26	.300	3,687	32.99	.551
FEP-2	1,819	76.17	< .001	3,815	2.40	.067	3,814	0.141	.935
SF-12 PH	1,789	2.23	.135	3,785	0.312	.816	3,784	0.319	.811
SF-12 MH	1,789	136.06	< .001	3,785	3.736	.011	3,784	0.972	.405

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Disclosures

Competing interests

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 and Hogrefe) on psychotherapy for chronic depression and on psychiatric emergencies. BM is employed as research director at GAIA AG, the company that developed, owns, and operates the internet intervention “Deprexis”. MH is a consultant of Servier. He was an invited speaker at several workshops and continuous education workshops over the last two years. All the other authors report no relationships with commercial interests.

Contributors

The principal investigators (TB, FH, JPK, BM and SM) designed the study and obtained funding. The EVIDENT study steering committee (TB, JPK, BM, SM, CS, and JS) further developed the study design in collaboration with the EVIDENT study group (steering committee and Wolfgang Greiner, Bielefeld; MH; WL; Matthias Rose, Berlin) and CG. Patient recruitment was coordinated by the EVIDENT study group. JPK conducted the statistical analyses with substantial input from EV. The results were interpreted by the steering committee with substantial input from the study group and CG. JPK wrote the manuscript with substantial input from the steering committee and CG. All authors commented on the manuscript and approved the final version.

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Data sharing statement

No additional data are available.

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Supplemental Table 1: Treatment utilization during the study period. Patients could use more than one treatment modality.

	Intervention *n* = 509 (50.1%)		Care as usual *n* = 504 (49.9%)		chi^2	*p*
Treatment between baseline and three months assessment						
Psychotherapy	127	32.3	140	35.1	0.767	.381
Outpatient psychiatric treatment	106	27.0	108	27.1	0.005	.941
Inpatient psychiatric treatment	5	1.3	9	2.3	1.123	.289
Antidepressant medication	193	48.9	204	51.3	0.455	.500
Treatment between three months and six months assessment						
Psychotherapy	118	31.3	119	31.7	0.016	.898
Outpatient psychiatric treatment	94	24.9	96	25.6	0.044	.833
Inpatient psychiatric treatment	6	1.6	9	2.4	0.629	.428
Antidepressant medication	192	50.8	192	51.2	0.012	.911

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	7
	2b	Specific objectives or hypotheses	8
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n.a.
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n.a.
Sample size	7a	How sample size was determined	10 / 15
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n.a.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Available in main publication
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Available in main publication
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	9
	11b	If relevant, description of the similarity of interventions	n.a.
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup	10

		analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Available in main publication
	14b	Why the trial ended or was stopped	n.a.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	17
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	20
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	20
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	20
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Available in main publication
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	8
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	5