

Anxiety and depression in patients who receive anti-VEGF treatment and the usability and feasibility of e-mental health support: the E-PsEYE pilot study

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Abstract

Purpose: E-PsEYE is an internet-based, guided self-help course, following the principles of cognitive behavioural therapy, to reduce anxiety and depression in patients with retinal exudative diseases who receive anti-vascular endothelial growth factor (anti-VEGF) treatment. The purpose of this study was to determine the prevalence and related factors of anxiety and depression in this population and evaluate the usability and feasibility of E-PsEYE.

Methods: Symptoms of anxiety and depression and related factors were determined in 90 patients (mean age 77 years, 58% female), based on multiple logistic regression analysis. Five patients with mild to moderate depression/anxiety tested the usability of E-PsEYE. They were asked to think aloud while completing two modules of the intervention and freely explore system features. The feasibility of the total E-PsEYE intervention was tested in 14 patients with mild to moderate depression/anxiety, based on a single arm pre-post study with a follow-up of three months: fidelity, acceptability, feasibility of study methods and potential effectiveness were explored.

Results: Fifty-three percent of the total study population experienced at least mild anxiety and/or depression symptoms. Especially female patients (odds ratio (OR) 3.89, 95% confidence interval (CI) 1.33–11.40), those who experienced limitations in daily life activities due to vision loss (OR 9.67; 95% CI 3.18–29.45) and those who experienced loneliness (OR 3.53, 95% CI 1.14–10.95) were more likely to have anxiety/depression. The usability study raised several possibilities for improvement, based on which E-PsEYE was improved. The feasibility study showed adequate fidelity and acceptability. Most participants were satisfied with the results (79%). There was a high response rate, no loss to follow-up and mental health problems decreased in more than half of the patients. The Wilcoxon signed rank test indicated lower post-test ranks compared to pre-test ranks (depression $Z = -1.34$, $p = 0.18$; anxiety $Z = -1.45$, $p = 0.15$).

Conclusions: Mental health problems are prevalent in patients who receive anti-VEGF treatment. Healthcare providers should recognise these problems and related factors in order to refer patients to appropriate care in a timely manner. Outcomes on the usability and feasibility of E-PsEYE are promising as a prelude to performing a randomised controlled trial, which will shed more light on its (cost-)effectiveness.

Introduction

Retinal exudative diseases, i.e., neovascular age-related macular degeneration, diabetic macular oedema, and macular oedema due to retinal venous occlusions comprise a major source of visual disability in older adults.^{1,2} These diseases are characterised by macular leakage leading to cystoid macular oedema, and ultimately to loss of visual acuity.

Pharmacological inhibition of vascular endothelial growth factor (anti-VEGF) can block the growth of neovascularisations and the leakage from newly formed or diseased vessels.^{3,4} Numerous studies have shown that treatment consisting of frequent intravitreal injections with anti-VEGF drugs (often monthly, sometimes for several years) has great potential for halting disease progression and significantly reduces patients' risk of severe visual impairment.^{3,4} Therefore, increasing numbers of patients receive this treatment. Based on general medical practitioner (GP) registrations, it is estimated that over 65,000 patients in the Netherlands received this treatment in 2020.⁵

However, it has also been recognised that there is a great variability in response to anti-VEGF treatment, where many patients do not respond or respond incompletely to the treatment.⁶ The uncertainty concerning treatment effects and the ongoing burden of frequent invasive intravitreal injections, may have negative consequences for patients' mental health.^{7,8} Previous studies showed that approximately one in three patients experienced at least mild symptoms of depression and/or anxiety.^{9–11} Senra *et al.*¹² found that 56% of patients reported anxiety related to anti-VEGF treatment, mainly caused by fear of going blind and concerns about treatment effectiveness.

To our knowledge, no previous studies have been published that aimed to treat mental health problems in this population, for which we believe e-mental health (i.e., using the internet to deliver mental health treatment) with guidance from a therapist may be a promising tool. Different studies have shown that internet-based guided cognitive behavioural therapy (CBT) can be effective in treating mental health problems.^{13,14} CBT is a widely used and effective type of psychotherapy to improve mental health,¹⁵ focusing on the development of personal coping strategies and changing unhelpful patterns in cognitions, emotions and behaviour. Research shows that online CBT can be as effective as face-to-face treatment,^{16,17} with the additional benefits of anonymity, accessibility, independence of time and place (i.e., it can be used by patients and therapists at any time and any place), and the relatively low input that is needed from professionals.

Therefore, a CBT-based guided e-mental health intervention for people who receive anti-VEGF treatment for retinal

exudative diseases (called E-PsEYE) was developed. This intervention was based on a guided self-help course for visually impaired patients from low vision service centres, and found to be effective as part of a stepped-care programme.¹⁸ It was modified for patients who received anti-VEGF treatment and implemented as a guided e-mental health intervention with attention on the particular sensorial needs of the target population. The aim of the present study was to determine the prevalence and related factors of anxiety and depression in patients who received anti-VEGF treatment in a cross-sectional study and to determine the usability and feasibility of the E-PsEYE intervention in a pilot study as a prelude to performing a randomised controlled trial (RCT).

Methods

Design

A cross-sectional study ($n = 90$) was performed to determine the prevalence and related factors of anxiety and depression in patients (≥ 50 years) who received anti-VEGF treatment. In addition, a pilot study was performed to determine the usability and feasibility of E-PsEYE, and make improvements based on input from the end-users. To determine the usability, a qualitative study was performed ($n = 5$), whereas for assessing feasibility ($n = 14$) a prospective one-group pre-test/post-test study was conducted.

Intervention

E-PsEYE is an internet-based, individually offered guided self-help course, based on the principles of CBT. The intervention was based on an effective guided self-help course to reduce depression and anxiety in visually impaired patients from low vision service centres.¹⁸ A project team (i.e., patient representatives ($n = 2$), social workers from low vision services ($n = 2$), ICT specialist ($n = 1$), ophthalmologists ($n = 2$) and researchers ($n = 2$)) modified this intervention for patients who received anti-VEGF treatment and changed it to an e-mental health intervention, with attention on the particular sensorial needs of the target population. The course consists of nine modules: (1) an introductory model containing information and psychoeducation; and eight follow-up modules: (2) uncertainty surrounding anti-VEGF injections; (3) depression and anxiety; (4) fatigue and stress; (5) participating in pleasurable activities; (6) replacing self-defeating thoughts with healthier thoughts; (7) identifying and replacing negative thought patterns; (8) identifying and replacing negative communication styles and (9) setting goals for the future. During the course, patients learn to deal with symptoms of depression and anxiety by applying various cognitive and behavioural techniques and skills. Special attention is paid to dealing

with uncertainty of progressive vision loss, adaptation to vision loss, participation in activities and seeking social support. A module takes approximately 30 min to complete and consists of an introduction, discussion of the previous module, new theory, examples and exercises. It is offered via the internet on a platform called Minddistrict (minddistrict.com). Patients can use it at home on a computer, laptop, smartphone or any electronic device that has internet access. Two experienced social workers from Royal Dutch Visio (a Dutch low vision service organisation) were trained (6 h in total) to guide patients in following the intervention. The training they received was adapted from that provided for the intervention that was previously found to be effective,¹⁸ during which information on mental health problems in this specific target population, motivational techniques and digital/telephone guidance was provided, and social workers were able to practice (role play) and discuss hypothetical cases. Guidance was provided digitally or by telephone, depending on patients' preferences and needs. It was estimated that patients would be able to finish the intervention within three months.

Participants

Inclusion criteria for the cross-sectional study to determine the prevalence and related factors of depression and anxiety were: (1) patients were 50 years or older; (2) they were diagnosed with retinal exudative disease (i.e., neovascular (wet) age-related macular degeneration (wAMD), diabetic macular oedema (DME) or macular oedema caused by retinal vein occlusion (RVO); (3) they were treated with anti-VEGF treatment and (4) they were able to speak the Dutch language adequately. For the pilot study, patients additionally: (5) had at least mild symptoms of depression and/or anxiety (a score of ≥ 5 on the Patient Health Questionnaire (PHQ)-9,¹⁹ and/or a score of ≥ 3 on the Hospital Anxiety and Depression Scale – Anxiety (HADS-A))²⁰ and (6) had access to the internet. Exclusion criteria were: (1) patients were cognitively impaired, which was assessed by telephone with the six-item Mini Mental State Examination (score < 3)²¹ and (2) patients had severe depression (score of ≥ 20 on the PHQ-9).

Procedure cross-sectional study

In September 2016, 190 patients who received anti-VEGF treatment at the Ophthalmology Department of Amsterdam University Medical Centers, The Netherlands were approached by letter to participate in this study. They received an information letter and an informed consent form. When patients agreed to participate, they received additional information from the research team by telephone. Based on this information, written informed

consent was obtained. Participants did not receive an incentive for their participation. Written questionnaires (with guidance by telephone if needed) were used to collect the data for the cross-sectional study. Subsequently, a heterogeneous group of eligible participants were chosen to participate in the pilot study.

The study protocol was approved by the Medical Ethics Committee of Amsterdam University Medical Centers, The Netherlands and has been conducted according to the tenets of the Declaration of Helsinki and the Dutch Medical Research Involving Human Subjects Act (WMO).

Procedure pilot study: usability

To determine the usability of the design of the internet-based e-mental health application for this target population, five participants were asked to follow the first two modules of the intervention at the low vision service centre. This number of participants is recommended for usability studies; more participants provide little additional benefits.²² At the start, participants were asked to think aloud while completing the modules and freely explore the system features either using a computer, laptop or any other electronic device. The same three researchers were present during each session. One researcher explained the study procedures to each participant and performed the semi-structured interview after the participant had completed the modules and explored the system features. This interview contained 12 questions, e.g., 'What do you think about the design of the website?', 'What do you think about the structure of the modules?', 'What can be done to improve the intervention?' The other two researchers closely observed what the participant said and did. In addition, all sessions were recorded on video-tape with the participant's consent. After each session the two researchers filled out an observation form together, with several questions (e.g., on the patient's behaviour, facial expressions) based on a discussion and close review of the recordings.

Procedure pilot study: feasibility

After improving the intervention based on the usability study, 14 participants were asked to follow the complete E-PsEYE intervention at home with guidance from a social worker as to determine the feasibility of implementing E-PsEYE in practice (primary) and the feasibility of study methods and potential effectiveness (secondary) of the intervention. Fourteen participants were deemed sufficient to perform a pilot study with the main aim of examining the feasibility of E-PsEYE as a prelude to performing an RCT, which is in line with recommendations from the literature.^{23–25} At baseline and after three months follow-up,

data were collected based on telephone interviews with patients and an evaluation form for social workers.

Outcome measures

Cross-sectional study

Symptoms of depression and anxiety were measured with the PHQ-9 and HADS-A,^{19,20} respectively, as the primary outcome measures. The PHQ-9 is based on nine questions on a 4-point Likert scale, ranging from 0 (not at all) to 3 (nearly every day). Total scores range from 0–27, with a cut-off score of 5 or higher indicating mild depression. The PHQ-9 has been widely used and is considered a valid and reliable instrument to measure depression in people with visual disability.¹⁹ The HADS-A has seven items on a 4-point Likert scale, with total scores ranging from 0 to 21 and a cut-off score of 3 or higher for mild anxiety. The reliability of the HADS-A is reported to be 'good to very good' in older adults.²⁰

Information on eye diseases, treated eye(s), logMAR binocular visual acuity, logMAR visual acuity over the last three check-up appointments, number of received injections and the duration of anti-VEGF treatment were derived from patients' medical files. In addition, the following patient-reported characteristics were gathered: gender, age, country of birth, employment, education, living alone or with others, receiving social support when needing help, satisfaction with social support, contact with persons who share similar experiences, loneliness, somatic comorbidity (i.e., chronic obstructive pulmonary disease/asthma, osteoarthritis, rheumatoid arthritis, peripheral arterial disease, diabetes mellitus, cardiac disease, cerebrovascular accident or stroke, cancer, other comorbid disorders),²⁶ history of mental health problems, received support from low vision services, subjective estimation of eyesight, experienced limitations in daily life activities because of vision loss, satisfaction with the anti-VEGF treatment effect, expectations and insecurity of future injections and the overall experience with the treatment. Furthermore, adaptation to vision loss was measured with the Adaptation to Vision Loss (AVL) scale with nine questions on a 4 point Likert scale, adapted from the AVL-12.²⁷ Total scores range from 0 to 27 with higher scores indicating more difficulty with adaptation.

Pilot study

To determine the feasibility of implementing E-PsEYE in practice, fidelity to the intervention was measured based on the duration of the intervention, duration of each module, number and nature (i.e., digitally or by telephone) of contacts with social workers. In addition, acceptability was measured based on the satisfaction of patients and social workers with the intervention. The Dutch Mental

Healthcare (MH) thermometer of satisfaction was used to measure patient satisfaction. This is a widely used questionnaire providing information on patients' satisfaction on provided information (e.g., 'Did you receive enough information about the expected result?'), relationship with the social worker (e.g., 'Did you feel comfortable with the social worker?') and results of the treatment (e.g., 'Did the intervention help you get on?').²⁸ Also, social workers were asked if they thought the intervention suited the needs of patients and they provided feedback on how to improve the intervention. Questions asked were: 'For how many patients did you think the intervention was / or was not the right approach and could you explain this?' 'What do you think needs to be improved about the intervention?', and 'Do you have any additional feedback on the treatment or supervision?'

To determine the feasibility of the study methods, recruitment rates, non-response and follow-up rates were determined. In addition, potential effectiveness of the programme based on 3-month changes in depression, anxiety and adaptation to vision loss (measured with the PHQ-9, HADS-A and AVL questionnaire, respectively) were determined.

Statistical analysis

All data were entered into Blaise data entry software (CBS, blaise.com) and converted into the statistical software package SPSS for Windows version 26 (IBM, ibm.com) for the analyses. Descriptive statistics on depression, anxiety and (satisfaction with) anti-VEGF treatment were examined. To analyse potential related factors of having at least mild depression and/or anxiety in this population, univariate logistic regression analyses were performed. All statistically significant ($p \leq 0.05$) independent variables were then included in a multiple logistic regression analysis, with a backward stepwise procedure. Variables were checked for multicollinearity, and linearity in case of continuous variables.

Data from the usability pilot study were analysed qualitatively: a thematic approach was used by the three researchers that performed the data collection (i.e., 'think aloud' method, semi-structured interviews and observations) to determine (the severity of) encountered problems, comments and recommendations. Analysis of feasibility outcomes was primarily based on descriptive statistics. Qualitative data from evaluation forms were analysed based on a thematic approach. Since data were not normally distributed in this small sample, the potential effectiveness of the programme was explored using the Wilcoxon signed rank test to determine differences in mild to moderate depression and anxiety symptoms in patients before and after the intervention.

Results

Participant flow

Of the 190 invited participants, non-responders ($n = 98$, 52%) were significantly younger than responders ($n = 92$, 48%) (mean difference 4.2 years; $p < 0.02$). The main reasons for non-response were: patients experienced no benefit for themselves, they did not experience mental complaints, they were too busy or they experienced their eye disease as too much of a burden to participate. Two participants were excluded because they did not speak the Dutch language, leading to a total of 90 participants. Of the participants with at least mild depression and/or anxiety who had internet access ($n = 40$), a heterogeneous group of 19 participants were asked to participate in the usability and feasibility pilot study, of whom five were assigned to the usability pilot study and 14 to the feasibility pilot study (Figure 1). Two participants declined participation in the pilot study (the first due to a busy schedule and the second due to hospitalisation); other participants were asked to take their place.

Patient characteristics

More women (58%) than men participated in the cross-sectional study ($n = 90$) and the mean age was almost 77 years (Table 1). Most of the participants judged their eyesight to be good or fair (76%). The mean logMAR

binocular visual acuity was 0.23. On average, participants had received 25 injections and were treated for almost 4 years, in most cases for only one eye (63%). During the last three check-ups, visual acuity of the treated eye improved in 41% of the participants, but visual acuity deteriorated in the same number of participants (41%). About 47% experienced limitations in daily life due to vision loss, 87% received social support and 42% experienced loneliness. On a scale from 1 (not satisfied) to 10 (very satisfied), participants rated their satisfaction with the anti-VEGF treatment effect as 7.3 (SD 1.9), and rated the expected beneficial effect of future treatment as 7.1 (SD 2.0). Participants rated their experience of the overall treatment as 8.0 (SD 1.6) and their insecurity about the treatment effect of future injections as 4.6 (SD 2.5).

In the usability pilot study ($n = 5$), four women and one man participated (Table 1). The mean age was 75 years, four out of five participants were born in the Netherlands, three lived alone, three had wAMD and two had DME. In the feasibility pilot study ($n = 14$), 43% were female, participants were on average 79 years old, 93% were born in the Netherlands, 50% lived alone and 57% had wAMD (Table 1).

Cross-sectional study

For all participants ($n = 90$), 39% met the cut-off score of ≥ 5 of the PHQ-9 for mild depression and 46% met the cut-

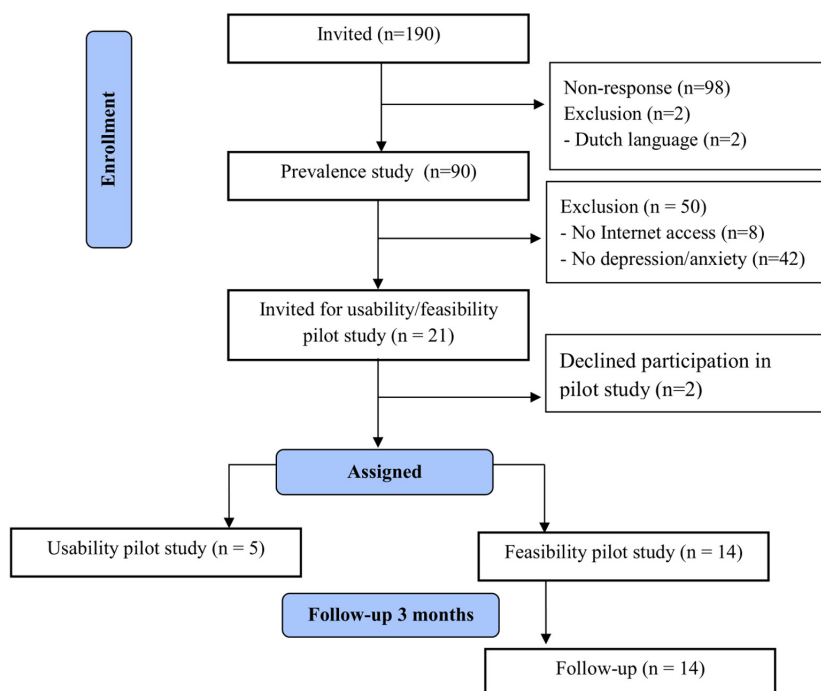


Figure 1. Overview of the study design and patient flow.

Table 1. Patient characteristics

Variables		Cross-sectional study	Usability pilot	Feasibility pilot Baseline	Feasibility pilot After 3 months
Gender (female)	N (%)	52 (57.8)	4 (80)	6 (42.9)	
Age (years)	Mean (SD)	76.6 (10.7)	75.0 (8.7)	78.5 (9.6)	
	Median [range]	77 [52–94]	72 [65–86]	81.5 [57–91]	
Country of birth (The Netherlands)	N (%)	79 (87.8)	4 (80)	13 (92.9)	
Employment (yes)	N (%)	17 (18.9)	1 (20)	4 (28.6)	
Education (years)	Mean (SD)	11.2 (3.6)	12.4 (3.4)	11.6 (4.1)	
	Median [range]	11 [0–16]	11 [9–16]	12 [0–16]	
Living alone (yes)	N (%)	44 (48.9)	3 (60)	7 (50)	
Somatic comorbidity	No comorbidity, N (%)	27 (30.0)	1 (20)	5 (35.7)	
	1 comorbid disorder, N (%)	31 (34.4)	4 (80)	3 (21.4)	
	≥ 2 comorbid disorders, N (%)	27 (30.0)	0 (0)	6 (42.9)	
Eye disease	wAMD, N (%)	60 (66.7)	4 (80)	8 (57.1)	
	DME, N (%)	16 (17.8)	1 (20)	2 (14.3)	
	Macula oedema due to RVO, N (%)	14 (15.6)	0 (0)	4 (28.6)	
Treated eye	Left, N (%)	33 (36.7)	2 (40)	5 (35.7)	
	Right, N (%)	24 (26.7)	1 (20)	4 (28.6)	
	Both, N (%)	33 (36.7)	2 (40)	5 (35.7)	
LogMAR binocular visual acuity	Mean (SD)	0.23 (0.26)	0.19 (0.21)	0.22 (0.25)	
	Median [range]	0.15 [0.0–0.9]	0.22 [0.0–0.5]	0.13 [0.0–0.8]	
Eyesight, subjective	Good, N (%)	29 (32.2)	1 (20)	5 (35.7)	
	Fair, N (%)	39 (43.3)	3 (60)	6 (42.9)	
	Poor, N (%)	22 (24.4)	1 (20)	3 (21.4)	
	Completely Blind, N (%)	0 (0.0)	0 (0)	0 (0)	
LogMAR visual acuity difference of treated eye between last three check-ups	Mean (SD)	0.03 (0.37)	−0.05 (0.04)	0.14 (0.59)	
	Median [range]	0.0 [−1.3 to 1.3]	−0.06 [−0.08 to 0.0]	0.01 [−0.36 to 1.30]	
Course of visual acuity in treated eye	Worsened, N (%)	23 (41.1)	2 (40)	6 (42.8)	
	Improved, N (%)	23 (41.1)	2 (40)	6 (42.8)	
	Stable, N (%)	10 (17.9)	1 (20)	2 (14.3)	
Duration of treatment (years)	Mean (SD)	3.8 (2.1)	3.0 (1.0)	1.9 (1.8)	
	Median [range]	3.7 [0.1–7.8]	3.9 [2.4–4.4]	2.5 [0.1–4.8]	
Time between check-ups (months)	Mean (SD)	5.2 (3.5)	4.9 (3.3)	5.4 (3.8)	
	Median [range]	5 [2–30]	5 [1–18]	6 [2–30]	
Amount of received injections	Mean (SD)	25.3 (17.8)	19.4 (11.6)	20.6 (17.5)	
	Median [range]	22 [2–81]	15 [8–35]	18 [2–57]	
Satisfaction with treatment effect†	Mean (SD)	7.3 (1.9)	7.1 (1.25)	7.1 (2.1)	
	Median [range]	8.0 [2–10]	7.5 [5–8]	7.5 [2–9]	
Expected profit of future injections‡	Mean (SD)	7.1 (2.0)	6.3 (1.20)	7.1 (2.2)	
	Median [range]	7 [1–10]	6 [5–8]	7 [3–10]	
Insecurity about future injection-effect‡	Mean (SD)	4.6 (2.5)	4.6 (1.67)	4.0 (2.0)	
	Median [range]	5 [1–10]	5 [2–6]	3 [1–8]	
Experience of total treatment‡	Mean (SD)	8.0 (1.6)	7.8 (1.10)	8.1 (1.5)	
	Median [range]	8 [1–10]	8 [6–9]	9 [4–10]	
Experiences limitations in daily life due to vision loss (yes)	N (%)	42 (46.7)	2 (40)	5 (35.7)	
Receives social support (yes)	N (%)	78 (86.7)	4 (80)	11 (78.6)	
Satisfied with social support (yes)	N (%)	56 (62.2)	3 (60)	7 (50)	
Contact with other patients (yes)	N (%)	18 (20)	0 (0)	6 (42.9)	

(continued)

Table 1. (continued)

Variables		Cross-sectional study	Usability pilot	Feasibility pilot Baseline	Feasibility pilot After 3 months
Loneliness (yes)	N (%)	38 (42.2)	4 (80)	7 (50)	
History of mental health problems (yes)	N (%)	13 (14.4)	1 (20)	2 (14.3)	
Received support from low vision services (yes)	N (%)	15 (16.7)	2 (40)	2 (14.3)	
Adaptation to vision loss	Mean (SD)	6.1 (6.7)	7.8 (7.8)	5.2 (6.3)	
	Median [range]	3 [0–25]	9 [0–18]	3 [0–19]	
Depression (PHQ-9)	No depression (score 0–4), N (%)	55 (61.1)	2 (40)	5 (35.7)	9 (64.3)
	Mild depression (score 5–9), N (%)	23 (25.6)	1 (20)	8 (57.1)	4 (28.6)
	Moderate depression (score 10–14), N (%)	5 (5.6)	1 (20)	1 (7.1)	1 (7.1)
	Moderately severe depression (score 15–19), N (%)	6 (6.7)	1 (20)	0 (0)	0 (0)
	Severe depression (score ≥20), N (%)	1 (1.1)	0 (0)	0 (0)	0 (0)
Anxiety (HADS-A)	No anxiety (score 0–2), N (%)	49 (54.4)	0 (0)	0 (0)	3 (21.4)
	Mild anxiety (score 3–7), N (%)	30 (33.3)	4 (80)	13 (92.9)	11 (78.6)
	Moderate to severe anxiety (score ≥8), N (%)	11 (12.2)	1 (20)	1 (7.1)	0 (0)
At least mild depression and/or anxiety symptoms	N (%)	48 (53.3)	5 (100)	14 (100)	11 (78.6)
At least moderate depression and/or anxiety symptoms	N (%)	17 (18.9)	2 (40)	2 (14.3)	1 (7.1)

Patient characteristics for the cross-sectional study group ($n = 90$), the usability pilot study ($n = 5$), the feasibility pilot study ($n = 14$) at baseline and after 3 months.

DME, diabetic macular oedema; HADS-A, Hospital Anxiety and Depressions Scale – Anxiety; PHQ-9, Patient Health Questionnaire-9; RVO, retinal vein occlusion; SD, standard deviation; wAMD, wet age-related macular degeneration.

[†]Scale 1 to 10.

off score of ≥ 3 on the HADS-A for mild anxiety (Table 1). Combined, approximately 53% experienced at least mild depression and/or anxiety symptoms and 19% experienced moderate to severe depression and/or anxiety symptoms. Based on univariate logistic regression analysis, female gender, years of education, living alone, satisfaction with the anti-VEGF treatment effect, expected profit of future injections, overall experience with anti-VEGF treatment, experienced limitations in daily life activities due to vision loss, loneliness and adaptation to vision loss were significantly related to experiencing at least mild depression and/or anxiety symptoms (Table 2).

Based on multiple logistic regression analyses, we found that female patients, patients who experienced limitations in daily life activities due to vision loss and patients who experienced loneliness were significantly more likely to have (at least) mild depression and/or anxiety symptoms. The derived multivariable model explained 45.8% of the total variance of having at least mild anxiety/depression in this population (Nagelkerke's R^2). The Hosmer-Lemeshow test indicated no statistically significant difference between

predicted and measured outcomes ($p = 0.43$) in the derived model.

Pilot study: usability

Three participants followed the E-PsEYE intervention on a personal computer and two on a tablet, based on their personal preference. Four specific themes emerged from the usability study: (1) structure, (2) navigation between screens, (3) website layout and (4) content and exercises. We found a lack of structure in the website. There were too many options in the menus and sometimes the text on the buttons suggested the buttons to do something different than expected. For example one participant explained: 'The button 'start' doesn't mean start the module, instead it brings me back to the homepage, which is confusing.' The audio button, allowing the text on the website to be read out loud by a computer voice, was easy to find and used by three of the five participants. It was experienced as one of the positive features of the website. However, it was also reading the hidden text, which was confusing. In the

Table 2. Univariate and multiple logistic regression analysis on related factors for experiencing at least mild depression and/or anxiety symptoms ($n = 90$)

Variables	Univariate logistic regression		Multiple logistic regression (final model)	
	OR	95% CI	OR	95% CI
Gender (female)	4.88	1.98–12.02	3.89	1.33–11.40
Age (years)	1.00	0.97–1.04		
Country of birth (The Netherlands)	2.20	0.60–8.12		
Employment (yes)	0.55	0.19–1.60		
Education (years)	0.88	0.77–0.99		
Living alone (yes)	2.75	1.17–6.47		
Somatic comorbidity (1 or more)	1.33	0.53–3.31		
Eye disease (wAMD)	1.22	0.51–2.94		
Treated eyes (both)	1.31	0.55–3.11		
LogMAR binocular visual acuity	2.00	0.22–17.97		
Eyesight, subjective (bad)	2.21	0.80–6.10		
LogMAR visual acuity difference of treated eye between check-ups	2.16	0.35–13.2		
Course of visual acuity in treated eye (worsened)	1.77	0.59–5.28		
Duration of treatment in years	0.99	0.81–1.21		
Time between check-ups in months	1.00	0.88–1.34		
Amount of received injections	0.98	0.96–1.00		
Satisfaction with treatment effect†	0.69	0.54–0.90		
Expected profit of future injections†	0.77	0.61–0.98		
Insecurity about future injection-effect†	1.07	0.90–1.28		
Experience of total treatment†	0.71	0.52–0.98		
Experiences limitations in daily life due to vision loss (yes)	8.07	3.10–21.00	9.67	3.18–29.45
Receives social support (yes)	0.55	0.13–2.38		
Satisfied with social support (yes)	0.39	0.15–1.00		
Contact with fellow-sufferers (yes)	1.12	0.40–3.16		
Loneliness (yes)	3.81	1.55–9.35	3.53	1.14–10.95
History of mental health problems (yes)	3.42	0.87–13.40		
Received support from low vision services (yes)	2.82	0.83–9.67		
Adaptation to vision loss	1.22	1.10–1.34		

Bold is significant at $p \leq 0.05$.

CI confidence interval; OR odds ratio; wAMD wet age-related macular degeneration.

†Scale 1 to 10.

navigation between screens, the legend was not read by four out of five participants, which lead to confusion. This was due to a lack of colour contrast (i.e., white text in a green bar) which was hard to read for most users; black on white or blue on yellow provides more contrast. In general, the layout: font style and size (i.e., Arial 14) and headers were positively experienced. A participant said: 'I can read it well due to the large font size and clear headers.' One participant used the magnification/zoom function on his computer (which can also easily be used on a tablet) and experienced no problems in doing so. At the beginning of each module a large picture was presented (half screen) which was experienced as a positive feature by four out of five participants. One participant could not see the pictures very well and therefore perceived it as having no added value. In every module a video was provided to explain some of the content. All participants were able to turn on

the video and found it had additional value to the written text; one participant could not see the video very well. The white background, calm voice and friendly appearance of the person on the video were experienced positively. However, the audio of one of the videos was of poorer quality and should be improved. Overall, the participants found the content of the modules interesting. However, the personal stories were not always relevant to them. Also, the exercises were not perceived as exercises by one of the participants, causing this user to think he did not do anything by following the modules.

Pilot study: feasibility

In the feasibility pilot study ($n = 14$), there was no loss to follow-up after 3 months. The median time it took participants to follow the intervention was 10 weeks (range 6–

16 weeks); only one participant exceeded 3 months due to hospitalisation for a condition unrelated to the intervention. The median time it took participants to complete a module was 35 min (range 20 to 65 min), with no apparent differences between modules. The median number of contacts between the social workers and patients was six (43% digitally and 57% by telephone). Most patients were satisfied with the information they received (71%), the social worker who supported them (86%) and the results of the treatment (79%). Social workers thought E-PsEYE was the right approach for patients in 71% of the cases. Based on specific feedback they provided on treatment and supervision, we were able to optimise our intervention.

In eight participants (57%), depression scores on the PHQ-9 reduced following the intervention by an average of 1.2 points (range -7 to 2). Four participants (28%) had no symptoms of depression after following the intervention (Table 1). In seven participants (50%) the HADS-A anxiety scores reduced after 3 months follow-up by an average of 0.7 points (range -4 to 2). Three participants (21%) did not experience anxiety symptoms following the intervention (Table 1). The Wilcoxon signed rank test indicated lower post-test ranks on depression compared to pre-test ranks ($Z = -1.34$, $p = 0.18$). Also for anxiety lower post-test ranks were found ($Z = -1.45$, $p = 0.15$). For adaptation to vision loss a smaller difference was found between pre-test and post-test ranks ($Z = -0.36$, $p = 0.72$).

Discussion

This study shows that symptoms of anxiety and depression are highly prevalent in patients who receive anti-VEGF treatment, which is in line with previous studies.^{9,11,12,29} More than half of the patients experience symptoms of at least mild anxiety and/or depression and 19% experience moderate to severe anxiety and/or depression symptoms.

In addition, we included a comprehensive assessment of a range of potential predictor variables. We found that women, patients who experience limitations in daily life activities due to vision loss and patients who experience loneliness tend to have depression/anxiety symptoms. These findings are in line with previous studies, in which female sex was found to be a risk factor for mental health problems,^{30,31} and limitations in daily life activities largely explained the association between visual impairment and mental health.^{9,11,30,32-34} Subjective loneliness, or the perceived absence of positive social relationships, has less often been investigated in people with vision loss,³⁵ but seems to be an important predictor to include. About 42% of patients experienced loneliness, which is high compared to the elderly in general, with prevalence estimates of 25% to 35%.^{36,37}

Binocular visual acuity and visual acuity difference of the treated eye were not found to be predictors of anxiety/

depression, while other studies did find an association between visual acuity and mental health in this population.^{9,29} This may be due to the fact that most patients in our study population had received anti-VEGF treatment for a long period of time (3.8 years on average). Visual acuity is expected to be more stable in this group.

The explained variance of the model was almost 46%, which is quite high compared with previous studies.^{30-32,38,39} This indicates that the predictor variables found, explain a large fraction of the variance in anxiety/depression between individual patients. However, the cross-sectional results give no indication of the sequence of events. Therefore, it is not possible to infer causality between the identified predictor variables and anxiety/depression. Future studies need to determine if these factors actually lead to change in mental health over time.

Healthcare providers, e.g., ophthalmologists, optometrists and supportive staff, should be aware of the high prevalence of anxiety/depression in this patient group and the proposed risk factors to be able to recognise these symptoms and refer patients timely to appropriate care. Currently, however, mental healthcare is often not received by patients; in our population only 17% had been in contact with low vision services where mental healthcare can be received. They are often not referred to these services since they still have fair to good vision. Not receiving the appropriate care may cause mild anxiety/depression symptoms to develop into full-blown disorders,⁴⁰ and generate substantial economic burden due to increased healthcare utilisation and productivity losses.⁴¹⁻⁴³

Within the E-PsEYE intervention that we developed, special attention is paid towards dealing with uncertainty of progressive vision loss, adapting to limitations caused by vision loss and reducing loneliness to address the risk factors for anxiety/depression in this population. Moreover, with this intervention we investigated the possibility for e-mental health support for this patient group. While assistive technologies (e.g., magnification of text, electronic book players, personal digital assistants) have already removed many barriers for people with visual disability,⁴⁴ e-mental health support has received little attention. An important reason for this is that the visual disability puts a particular challenge on the usability and feasibility of receiving e-mental health care. In our usability pilot study we found several important aspects that need to be considered to offer an accessible intervention, e.g., the website structure should be very basic and clear/intuitive, good audio support and magnification options should be provided and large pictures and videos may have added value. Based on our findings, we were able to make the intervention accessible for patients: i.e., cosmetically and content wise and by adding specific instructions/training for patients.

The feasibility pilot study showed adequate fidelity and acceptability of the intervention. Most participants were satisfied with the results of the intervention, the information they received and their contact with the social worker who supported them. Also, therapists thought the intervention suited the needs of patients in most cases. This is comparable to the experienced satisfaction of visually impaired patients from low vision service centres who followed a similar intervention on paper and Daisy compact disc as part of a stepped-care programme.¹⁸ In addition, there was a high response rate and no loss to follow-up. Anxiety decreased in half of the patients by an average of 0.7 points, and depression decreased in more than half of the patients with an average of 1.2 points. Based on previous studies in people with visual impairment,^{18,45} these reductions may be considered as clinically relevant. The Wilcoxon signed rank test also showed a decrease in anxiety and depression following the intervention (anxiety $Z = -1.45$, $p = 0.15$; depression $Z = -1.34$, $p = 0.18$). Based on an α of 0.05, these differences would not be considered statistically significant. However, these outcomes are based on a small sample size ($n = 14$) and the non-parametric approach tends to have lower power, which yields less precise estimates and higher p -values. Therefore, these outcomes could still be considered promising and warrant a (sufficiently powered) RCT.

It should be noted that many patients who receive anti-VEGF treatment still have fair to good vision (i.e., in 75% of our study population, none were completely blind); therefore, different adaptations may be needed for patient populations with poorer vision. In addition, although we increased the usability of E-PsEYE to make it accessible for patients who receive anti-VEGF treatment and provided support for its feasibility, this does not imply that E-PsEYE is accessible for all anti-VEGF patients, since we only included patients who were willing to participate and had access to the internet. We may have missed patients who have more difficulties using a computer and patients who have difficulties in recognising or acknowledging their mental health problems. Also, we mostly included participants who had received anti-VEGF treatment for a longer period of time, who were accustomed to the treatment (i.e., less anxiety may be expected related to the treatment in this group) and for whom visual acuity may be more stable.

Future research should examine who is willing to participate in e-mental health treatments and who is not, and to differentiate between predictors and mediators regarding the outcome.

In conclusion, we can state that mental health problems are prevalent in patients who receive anti-VEGF treatment and that e-mental health support may provide a promising, accessible solution. Future results from an RCT will shed more light on the effectiveness of E-PsEYE and will also focus on its cost-effectiveness.

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Author contribution

Hilde PA van der Aa: Conceptualization (equal); Formal analysis (lead); Funding acquisition (lead); Investigation (lead); Methodology (lead); Project administration (lead); Writing-original draft (lead); Writing-review & editing (lead). **Ger HMB van Rens:** Conceptualization (supporting); Funding acquisition (supporting); Writing-original draft (supporting); Writing-review & editing (supporting). **Frank D Verbraak:** Conceptualization (supporting); Writing-original draft (supporting); Writing-review & editing (supporting). **Machteld Bosscha:** Conceptualization (supporting); Writing-original draft (supporting); Writing-review & editing (supporting). **Hannie C Comijs:** Conceptualization (supporting); Writing-original draft (supporting); Writing-review & editing (supporting). **Ruth MA van Nispen:** Conceptualization (equal); Funding acquisition (supporting); Investigation (supporting); Methodology (supporting); Supervision (equal); Writing-review & editing (supporting).

Disclosure

The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article.

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