Treatment course comparison between anxiety-related disorders in adult outpatients: a Leiden routine outcome monitoring study

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Treatment Course Comparison Between Anxiety-Related Disorders in Adult Outpatients

A Leiden Routine Outcome Monitoring Study

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Abstract: Anxiety-related disorders constitute the leading prevalent mental disorders, with major burden on patients, their relatives, and society. Moreover, there is considerable treatment nonadherence/nonresponse. We used routine outcome monitoring (ROM) data from outpatients covering four anxiety-related disorders (*DSM-IV-R*, $N = 470$) to examine their 6-month treatment course and its predictors: generalized anxiety disorder, panic disorder with agoraphobia, obsessive-compulsive disorder, and posttraumatic stress disorder. Measures included Mini-International Neuropsychiatric Interview Plus, Brief Symptom Inventory (BSI), Montgomery-Åsberg Depression Rating Scale (MADRS), Brief Anxiety Scale (BAS), and Short Form Health Survey 36 (SF-36). On the clinician-rated instruments (MADRS/BAS), all anxiety-related disorder groups showed a significant albeit modest improvement after treatment. On the BSI self-rating, only generalized anxiety disorder and posttraumatic stress disorder showed a significant modest improvement. No anxiety-related disorder groups improved significantly regarding SF-36 physical functioning. For BSI symptom course, significant predictors were comorbid somatoform/total disorders, SF-36 physical functioning/general health, and MADRS score. Clinical implications and future research recommendations are discussed.

Key Words: Treatment course, generalized anxiety disorder, panic disorder with agoraphobia, obsessive compulsive disorder, posttraumatic stress disorder

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Anxiety-related disorders are among the most common mental disorders in the world (*e.g.*, Bandelow and Michaelis, 2015; Otowa et al., 2016; Shimada-Sugimoto et al., 2015). According to large population-based surveys, up to 33.7% of the population is affected by an anxiety-related disorder during their lifetime (Gallo and Hulse, 2022; Kessler et al., 2012). As with depression, women are twice as likely to be diagnosed with an anxiety-related disorder compared with men (McLean et al., 2011; Pesce et al., 2015).

Anxiety-related disorders often lead to psychosocial and functional limitations and thus place a significant burden on patients, their relatives, and society (Ormel et al., 2008; Scholten et al., 2016; Yang et al., 2021). Economic costs of anxiety-related disorders soar due to productivity loss (Kaya et al., 2022) and increased health services use (Ormel et al., 2008). Hence, there is a growing consensus that both symptom remission and functional recovery are important parameters within research and treatment of anxiety-related disorders (Beard et al., 2010; De Beurs et al., 2021; Disabato et al., 2021; Hellström et al., 2021; Iancu et al., 2014).

This is all the more important because anxiety-related disorders are characterized by an increasing incidence rate (*e.g.*, Bandelow and Michaelis, 2015; Yang et al., 2021), early age of onset (Casey and Lee, 2015; Yang et al., 2021), debilitating nature (Bandelow and Michaelis, 2015), and high suicide attempt rate (Bentley et al., 2016; Chand and Marwaha, 2020; Kanwar et al., 2013). They are also often chronic and relapsing, leading to an unfavorable long-term course (*e.g.*, Bandelow and Michaelis, 2015; Scholten et al., 2013; Schopman et al., 2021). Compared with mood disorders, the course of anxiety-related disorders is characterized by more chronicity: 41% of patients with anxiety-related disorders have a chronic course, compared with 24.5% of patients with mood disorders (Penninx et al., 2011). Moreover, anxiety-related disorders are highly comorbid with other mental disorders such as depression (*e.g.*, Bandelow and Michaelis, 2015; Kessler et al., 2003; Penninx et al., 2021; Saha et al., 2020; Ter Meulen et al., 2021) or bipolar disorder (*e.g.*, Spoorthy et al., 2019). This comorbidity may adversely impact treatment outcome for anxiety-related disorders (Olatunji et al., 2010).

Anxiety-related disorder treatment consists of psychotherapy, pharmacotherapy, or a combination of both, according to (inter)national guidelines (*e.g.*, Chand and Marwaha, 2020). Cognitive behavioral therapy (CBT) is considered the most effective and criterion standard psychotherapy for anxiety-related disorders (Carpenter et al., 2018; Hofmann and Smits, 2008; Levy et al., 2021; Szuhany and Simon, 2022), due to its triple focus (on behavior, feelings, cognitions) and various effective elements (*e.g.*, exposure, activation, cognitive restructuring, relaxation, problem solving) (*e.g.*, Bandelow et al., 2015; Bogucki et al., 2021; Chand and Marwaha, 2020; Cooper et al., 2022; Kaczkurkin and Foa, 2015; Shepardson et al., 2018). However, it should be noted that a significant percentage of patients do not reach remission after CBT (*e.g.*, Springer et al., 2018; Vieira et al., 2022) or they relapse (*e.g.*, Levy et al., 2021; Lorimer et al., 2021). Other patients find it difficult to tolerate or adhere to treatment and stop prematurely (*e.g.*, Taylor et al., 2012). Finally, a significant percentage of patients with anxiety-related disorders do not show a favorable long-term outcome, because they transition to residual anxiety symptoms or to another diagnostic category (Scholten et al., 2016; Schopman et al., 2021). Researchers have identified several factors that affect CBT outcomes such as, for example, dose of therapy, homework compliance, how exposure is conducted, and clinician adherence to evidence-based practice (*e.g.*, Cooper et al., 2022).

In this context, treatment course and its prediction are important aspects (*e.g.*, Batelaan et al., 2014; Carlier et al., 2018; Hendriks et al., 2013; Phillips et al., 2013). Determining appropriate clinical responses based on a likely course of anxiety-related disorders requires further research. This is especially the case in secondary mental health care, where comparative treatment course studies between different anxiety-related disorders in adult patients are scarce, representing a knowledge gap. After all, most anxiety-related studies on the course of treatment involve a single anxiety disorder (*e.g.*, Herzog et al., 2022; Hunt et al., 2022;

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Probst et al., 2022), and the occasional studies that do compare treatment course of different anxiety-related disorders mainly concern a combined sample (depressive and anxiety disorders, *e.g.*, Rayner et al., 2022; participants with and without treatment, *e.g.*, Spinhoven et al., 2016).

In line with this aforementioned knowledge gap, the dual purpose of our study was to a) compare treatment course outcome (*i.e.*, symptom remission and functional recovery) between different anxiety-related disorders and b) investigate predictors of treatment course outcome regarding both symptoms and functioning. We used a naturalistic secondary mental health sample, based on routine outcome monitoring (ROM) data from psychiatric outpatients with the four most commonly present anxiety-related disorders in our data set (*i.e.*, generalized anxiety disorder, panic disorder with agoraphobia, obsessive-compulsive disorder, and posttraumatic stress disorder, diagnosed according to *DSM-IV-R* [American Psychiatric Association, 2000]). Based on our sample data set and the available relevant literature, we expected the following.

Regarding treatment course comparison, we expected that panic disorder with agoraphobia and obsessive-compulsive disorder would have the worst course; these disorders generally have a more chronic treatment course compared with other anxiety-related disorders (*e.g.*, Batelaan et al., 2014; Eisen et al., 2010; Hendriks et al., 2013; Kessler et al., 2005a, 2005b; Yonkers et al., 2003; Springer et al., 2018).

Regarding treatment outcome predictors, we expected that older age, absence of a life-partner, and being female could predict a less favorable treatment course (McLean et al., 2011; Penninx et al., 2011; Schopman et al., 2021; Ten Have et al., 2020; Springer et al., 2018). We also expected that higher baseline severity of anxiety symptoms would predict a poorer outcome (Asselmann and Beesdo-Baum, 2015; Batelaan et al., 2014; Boer et al., 2019; Hendriks et al., 2013; Hovenkamp-Hermelink et al., 2021; Schopman et al., 2021; Spinhoven et al., 2016). In addition, we thought that lower baseline functioning/disability and comorbidity would predict a poorer outcome (Batelaan et al., 2014; Bomyea et al., 2015; Bruce et al., 2005; Spinhoven et al., 2016; Taylor et al., 2012; Ten Have et al., 2020; Ter Meulen et al., 2021).

METHODS

Study Design

The treatment course of separate anxiety-related disorders and their predictors were examined 6 months after baseline (6-month follow-up study; Anstey and Hofer, 2004; Carlier et al., 2018).

Participants and Procedure

The study population consisted of 470 outpatients in secondary mental health care between 18 and 65 years of age with an anxiety-related disorder as the primary diagnosis and possible nonanxiety comorbid disorders. Previous research with our ROM data (*e.g.*, Schawo et al., 2019) and other studies (*e.g.*, Frostholm et al., 2015) showed that comorbidity in anxiety-related disorders relates primarily to other disorders (*e.g.*, depression, somatoform disorder). The latter was also the case in the current study: patients with the four most common anxiety-related disorders in our ROM data (generalized anxiety disorder [n = 111], panic disorder with agoraphobia [n = 120], obsessive-compulsive disorder [n = 95], posttraumatic stress disorder [n = 144]) had the registered anxiety-related disorder as the primary diagnosis, no comorbid anxiety-related disorder, and possibly other comorbid disorder(s) (see Table 1). Other anxiety-related disorders were not included in the analyses due to too small numbers and missing data. Given the focus of this study, patients with a primary diagnosis other than anxiety-related disorder were also not included in the analyses. Diagnostic information (*DSM-IV-R*; American Psychiatric Association, 2000) was based on both the Mini-International Neuropsychiatric Interview Plus 5.00 (MINI-Plus; see *Measures*) and clinical information (patients who were treated for anxiety-related disorder as their primary diagnosis). For the baseline characteristics of the study population, see Section 3.1 and Table 1.

Participants' data were gathered using a Web-based ROM program, in which patients were routinely assessed as part of the standard diagnostic procedure (Carlier et al., 2018; De Beurs et al., 2011; Van Noorden et al., 2012). The patients were referred by their general practitioner to the mental health care provider GGZ Rivierduinen (service area of 1.1 million inhabitants). The executor of this study was the Dutch Department of Psychiatry of the Leiden University Medical Center.

The main objective of ROM is to improve clinical practice using interim monitoring and evaluation of treatment progress for the individual patient (Carlier et al., 2012a, 2018; Kendrick et al., 2016; Lambert, 2017; Van Noorden et al., 2012). ROM measurements (duration 1–2 hours) can take place before (baseline), during, and after treatment. ROM continues for the duration of the patient's treatment and consists of a psychometric battery of instruments, both self-report and interviewer-based (De Beurs et al., 2011). This study focuses on baseline and a 6-month assessment—later data were insufficient and/or incomplete to use for research purposes. All interviewer-based measurements were administered by an independently trained assessor (psychiatric research nurse or psychologist). Quality control and calibration among assessors ensured that the quality was maintained during data collection (De Beurs et al., 2011). To prevent missing data, all measurements were completed on touch-screen computers. Patients with insufficient mastery of the Dutch language were ineligible. For more detailed information on the ROM procedure, see Carlier et al. (2012a, 2012b, 2014, 2018), De Beurs et al. (2011), De Klerk et al. (2011), and Van Noorden et al. (2012).

Participants received standard mental health treatment (administered by psychiatrists, clinical psychologists, or psychotherapists) according to the principle of stepped care, which is based on (inter)national evidence-based treatment guidelines and consists of psychotherapy (mostly CBT), pharmacotherapy, or a combination of both (Van Fenema et al., 2012a; Van Fenema et al., 2012b; Van der Lem et al., 2011; Van Noorden et al., 2012). Treatment was not assigned, controlled, nor influenced by the research team.

Measures

We focused on ROM data collected using five validated instruments (see below): MINI-Plus 5.00 (baseline only available), Montgomery-Åsberg Depression Rating Scale (MADRS), Brief Anxiety Scale (BAS), Brief Symptom Inventory (BSI), and the Short Form Health Survey 36 (SF-36). We chose these instruments because we wanted to a) measure functioning (SF-36) in addition to psychopathology, and b) use clinician-rated instruments (MADRS, BAS, and MINI-Plus) alongside patient-reported measures. To be able to analyze the largest possible sample size, we opted for data from generic instruments (standard in all patients, *e.g.*, BSI) and the follow-up measurement after 6 months of treatment (available in most patients) (Carlier et al., 2018).

Psychiatric Diagnoses

DSM-IV-R diagnoses were assessed using the Dutch translation of the MINI-Plus, which is an extended version of the original MINI (Sheehan et al., 1998; Van Vliet and De Beurs, 2007). It is a fully structured diagnostic interview that assesses *DSM-IV-R* criteria for the main psychiatric disorders (current/lifetime). Excellent interrater and test-retest reliabilities of the MINI and moderate validity of MINI versus CIDI and SCID-P have been reported (Lecrubier et al., 1997; Sheehan et al., 1998). At the time of our study, the MINI-Plus according to *DSM-5* criteria was not yet available.

Psychological Symptoms

- MADRS and BAS: Symptoms of anxiety and depression were measured using the observer-rated MADRS and BAS, which are both

TABLE 1. Baseline Sociodemographic and Clinical Characteristics for Total Anxiety-Related Disorders Group and the Four Separate Anxiety Disorder Groups

Patient Characteristics	Total $N = 470$	Generalized Anxiety Disorder $n = 111$	Panic Disorder $n = 120$	Obsessive-Compulsive Disorder $n = 95$	Posttraumatic Stress Disorder $n = 144$	p
Age, mean (SD)	41.43 (14.36)	44.47 (15.61)[a]	46.17 (15.32)[a]	38.85 (13.31)[b,c]	42.92 (13.46)[a,b]	0.000
Gender (%)						0.000
Male	34.5	39.6	35.8	31.6	21.5	
Marital status (%)				0.000		
Married	50.8	57.6	65	55.8	40	
Widow	11.5	15.3	12.5	8.4	20	
Not married	37.6	27	22.5	35.8	40	
Housing situation (%)					0.000	
Living alone	22.8	24.3	15	18.9	31.3	
With family	19.8	12.6	16.7	22.1	14.6	
With partner	54	49.5	63.3	54.7	41.7	
Educational status (%)					0.000	
Primary school	8.4	8.1	11.7	5.3	12.5	
Lower education	31	27	30.8	26.3	39.6	
Middle education	40	31.5	40	47.4	34	
High education	20.5	33.3	17.5	21.1	13.8	
Ethnicity (%)						0.000
Dutch	89.1	95.5	87.5	94.7	76.4	
Comorbidity no. disorders (%)					0.000	
0	12.3	18.9	10	32.6	9.7	
1	23.7	44.1	35.8	38.9	46.5	
2	27.7	26.1	30.8	18.9	31.9	
3	19.4	7.2	19.2	5.3	8.3	
>3	16.8	3.6	4.2	4.2	3.5	
Comorbidity type of disorders (%)				0.000		
Somatoform	11.2	15	13.4	10.5	8.3	
Mood	74.6	70	73.1	76.3	79.8	
Somatoform + mood	14.2	15	13.4	13.2	11.9	
BSI total, mean (SD)	1.18 (0.74)	1.17 (0.70)[a,b]	1.13 (0.72)[a]	0.97 (0.69)[a,b]	1.44 (0.84)[b]	0.000
BAS, mean (SD)	13.81 (6.51)	14.20 (7.23)[a,b]	14.44 (6.18)[a]	11.02 (5.76)[b]	15.42 (6.25)[a]	0.000
MADRS, mean (SD)	16.32 (9.28)	15. 54 (9.18)[a]	15.75 (9.48)[a]	13.67 (9.35)[a]	20.70 (8.53)	0.000
SF-36 total, mean (SD)	13. 89 (4.36)	13.30 (4.38)[a,b]	14.92 (4.06)[c,d]	12.96 (4.20)[a,c]	15.17 (4.27)[b]	**0.000**

Notes: Values in the same row with different superscript numbers are significantly different (post hoc comparison by Bonferroni test, $p < 0.01$). BSI, BAS, MADRS, and SF-36 total scores denote the baseline scores.

Significant p values ($p < 0.01$) are printed in bold.

Patients of the four separate anxiety disorder groups have the registered anxiety disorder but no other anxiety disorder(s).

Somatoform denotes comorbid somatoform disorder; MOOD denotes comorbid mood disorder; somatoform + mood denotes comorbid somatoform and mood disorders.

part of the abbreviated Comprehensive Psychopathological Rating Scale (CPRS). The CPRS is an interviewer-based instrument, and its interrater reliability has appeared at least as good as that of the Present State Examination (Goekoop et al., 1991). We chose the MADRS (Montgomery and Åsberg, 1979) and the BAS (Tyrer et al., 1984) because comorbidity of depression (and somatoform disorder) is common in people with anxiety-related disorders. The MADRS and the BAS are used to measure the severity of depression and anxiety, respectively. Both scales consist of 10 items that are scored on a seven-point scale, ranging from 0 (none) to 6 (often). The sum of the item scores ranges from 0 to 60. Higher scores represent worse depression or anxiety.

- BSI: The BSI is a 53-item self-report instrument that is used to assess psychopathological symptoms in several domains. It is an abbreviated version of the Symptom Checklist-90 (Derogatis et al., 1973). The BSI demonstrates high concordance with clinician symptom assessment and strong test-retest and internal consistency reliabilities. It includes nine symptom subscales (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism) and a total score (BSI total). BSI scores range from 0 (not at all) to 4 (extremely). The subscale and total scores are calculated as an average of the relevant items, with higher scores indicating more severe psychopathology (Derogatis et al., 1973; Derogatis and Melisaratos, 1983).

Functional Health Status

The self-report SF-36, derived from the Rand Medical Outcome Study (Aaronson et al., 1998; Ware et al., 1993), measures functional health status and well-being and can be used as a population-based assessment of quality of life. It has demonstrated high levels of reliability and validity (Karlsen et al., 2011). The SF-36 consists of 36 items divided into the subscales physical functioning, social functioning, role limitations due to physical health problems, role limitations due to emotional problems, vitality, bodily pain, general mental health, and general health perceptions (general health/total). The latter SF-36 subscale general health is often considered as the total scale for functional health (Karlsen et al., 2011; Pedersen et al., 2016; Schröder et al., 2012; Ware et al., 1993; Wortman et al., 2016; Zonneveld et al., 2012). Subscale scores are calculated as the sum of the relevant items, ranging from 0 to 100 (see also *Statistical Analyses*).

Statistical Analyses

First, all SF-36 subscales were inversely scored—higher scores imply a worse health state. In addition, all SF-36 subscales were transformed to a 100-point scale (range, 0–100; Ware et al., 1993). Baseline characteristics of the research groups were compared using a chi-square test, analysis of variance, and the Kruskal-Wallis test. Post hoc comparisons were performed with a Bonferroni adjustment to control for multiple testing (see Table 1).

Second, for treatment course regarding psychological symptoms (BSI, BAS, and MADRS) and functioning (SF-36), we used paired *t* tests to compare baseline versus at 6 months (see Tables 2–4, including effect sizes).

Third, to test the predictors for treatment course, we used the total group of anxiety-related disorders, thus keeping the sample size as large as possible. The four anxiety-related disorder groups were used as individual predictors. We used hierarchical multiple regression analysis to investigate predictors for the course of symptoms (BSI total; see Supplementary Material Table 5A, Supplemental Digital Content 1, http://links.lww.com/JNMD/A165) and predictors for the course of functioning (SF-36 physical functioning scale, based on Zonneveld et al., 2012; see Supplementary Material Table 5B, Supplemental Digital Content 1, http://links.lww.com/JNMD/A165). The course of symptoms was determined by the difference score of the BSI total (BSI total at 6 months minus BSI total at baseline). The course of functioning was determined by the difference score of the SF-36 physical functioning (SF-36 physical at 6 months minus SF-36 physical at baseline; Zonneveld et al., 2012).

Predictors were based on relevant literature (*e.g.*, Zonneveld et al., 2012) and their availability in our ROM database. We took several control variables into account for the course of symptoms: pretreatment BSI total, age, sex, and marital status (*e.g.*, Grant et al., 2014; Iezzoni, 2013; Karlsen et al., 2011; Ware et al., 1993; Zonneveld et al., 2012). Predictors for the course of symptoms included education, comorbid disorders (mood disorder, somatoform disorder, mood and somatoform disorder, total comorbid diagnoses), BAS, MADRS, SF-36 physical functioning, SF-36 social functioning, SF-36 general health, and the four separate anxiety-related disorder groups (*e.g.*, Pedersen et al., 2016; Schröder et al., 2012; Wortman et al., 2016; Zonneveld et al., 2012). Control variables for the course of functioning included pretreatment SF-36 physical functioning, age, sex, and marital status (Zonneveld et al., 2012). Predictors for the course of functioning included education, comorbid disorders (mood disorder, somatoform, mood and somatoform disorder, total comorbid diagnoses), BAS, MADRS, BSI total, and the four separate anxiety-related disorder groups.

Statistical analyses were performed using SPSS version 25. Significance was set at $p < 0.01$ (according to multiplicity guidelines of data/hypothesis/testing, *e.g.*, Carlier et al., 2018; Feise, 2002; Ranstam, 2016).

RESULTS

Baseline Sociodemographic and Clinical Characteristics of the Patients

Table 1 presents the baseline characteristics of the total group of anxiety-related disorders ($N = 470$) and the four anxiety-related disorder groups. The groups of anxiety-related disorders significantly differed in age, $F(5,661) = 8.90$, $p < 0.001$; BSI total, $F(5,661) = 5.70$, $p < 0.001$; BAS, $F(5,593) = 5.73$, $p < 0.001$; MADRS, $F(5,593) = 8.94$, $p < 0.001$; and SF-36 total, $F(5,660) = 6.83$, $p < 0.001$. In addition, sex, $\chi^2(5) = 71.42$, $p < 0.001$; marital status, $\chi^2(10) = 50.37$, $p < 0.001$; housing situation, $\chi^2(25) = 190.24$, $p < 0.001$; educational status, $\chi^2(15) = 101.80$, $p < 0.001$; ethnicity, $\chi^2(25) = 147.65$, $p < 0.001$; number of comorbid disorders, $\chi^2(25) = 153.49$, $p < 0.001$; and comorbid type of disorder, $\chi^2(10) = 39.14$, $p < 0.001$, were all significantly different between the groups (see Table 1). For instance, posttraumatic stress disorder patients, compared with the other three anxiety-related disorder groups, were mostly women, usually living alone, with the most mood comorbidity, and with the worst baseline scores regarding both symptoms (BSI, BAS, and MADRS) and functioning (SF-36). For further details on the baseline characteristics, see Table 1.

Baseline Against 6-Month Treatment Course of Psychological Symptoms (BSI, BAS, and MADRS) and Functioning (SF-36) for the Anxiety-Related Disorder Groups

These results are divided into three tables (Tables 2–4).

Table 2 shows the 6-month treatment course of the total group of anxiety-related disorders and generalized anxiety disorder.

For the total group of anxiety-related disorders, there was a significant but mostly small reduction at 6 months for BSI, MADRS, BAS, and most SF-36 subscales, except for the insignificant SF-36 physical functioning, pain, and general health subscales.

For the generalized anxiety disorder, there was a significant but mostly small reduction at 6 months for most subscales, except for the insignificant BSI somatization, hostility, and phobic anxiety subscales and the insignificant SF-36 physical functioning, social functioning, limitations physical, limitations emotional, pain, and general health subscales.

Table 3 shows the 6-month treatment course of panic disorder with agoraphobia and obsessive-compulsive disorder.

For panic disorder, there was a significant reduction at 6 months only for the BSI somatization subscale, the MADRS, and the BAS.

For obsessive-compulsive disorder, most of the scores showed an insignificant reduction at 6 months. Only the following scores had a significant reduction at 6 months: the BSI anxiety and psychoticism subscales; the SF-36 social functioning, limitations physical, limitations emotional, mental health subscales; and MADRS and BAS.

Finally, Table 4 shows the 6-month treatment course of posttraumatic stress disorder.

Patients with posttraumatic stress disorder showed a significant but mostly small reduction at 6 months for all the BSI subscales, MADRS, and BAS. For the SF-36, patients with posttraumatic stress disorder only showed a small significant reduction at 6 months for the mental health subscale.

In sum, regarding the four groups of anxiety-related disorders, the following can be said in terms of improvement at 6-month posttreatment regarding the core measurements of BSI total, MADRS, BAS, and SF-36 physical functioning: a) all groups showed a significant improvement of observer-rated severity of depression (MADRS) and anxiety (BAS), b) only generalized anxiety disorder and posttraumatic stress disorder (but not obsessive-compulsive disorder and panic disorder) showed a significant improvement of self-rated psychopathology (BSI total), and c)

TABLE 2. Six-Month Treatment Course of the Total Anxiety Disorders Group ($N = 470$) and the Generalized Anxiety Disorder Group ($n = 111$)

Patient Characteristics	Total Anxiety Disorders B	Total Anxiety Disorders 6 mo	*t*	*p*	Effect Size (*d*)	Generalized Anxiety Disorder B	Generalized Anxiety Disorder 6 mo	*t*	*p*	Effect Size (*d*)
BSI, mean (SD)										
Somatization	0.83 (0.77)	0.74 (0.75)	3.512	**0.000**	0.14	0.89 (0.80)	0.85 (0.88)	0.636	0.526	0.06
Obsessive-compulsive	1.52 (0.95)	1.32 (0.93)	5.609	**0.000**	0.22	1.56 (0.86)	1.32 (0.89)	2.767	**0.007**	0.26
Interpersonal sensitivity	1.54 (1.09)	1.27 (1.02)	7.081	**0.000**	0.27	1.45 (1.06)	1.17 (0.99)	3.005	**0.003**	0.29
Depression	1.47 (1.04)	1.21 (1.05)	6.248	**0.000**	0.24	1.48 (1.02)	1.20 (1.06)	2.662	**0.009**	0.25
Anxiety	1.34 (0.94)	1.12 (0.89)	5.893	**0.000**	0.23	1.46 (1.00)	1.15 (0.89)	3.099	**0.002**	0.30
Hostility	0.8 (0.78)	0.70 (0.76)	3.247	**0.001**	0.13	0.75 (0.69)	0.69 (0.82)	0.831	0.408	0.08
Phobic anxiety	1.05 (0.89)	0.85 (0.85)	5.972	**0.000**	0.23	0.79 (0.78)	0.67 (0.73)	1.634	0.105	0.16
Paranoid ideation	1.06 (0.89)	0.90 (0.82)	5.151	**0.000**	0.20	1.02 (0.84)	0.83 (0.84)	3.209	**0.002**	0.31
Psychoticism	1.15 (0.86)	0.94 (0.84)	6.485	**0.000**	0.25	1.11 (0.80)	0.89 (0.84)	2.897	**0.005**	0.28
Total score	1.19 (0.74)	1.00 (0.72)	6.84	**0.000**	0.26	1.17 (0.70)	0.98 (0.74)	2.954	**0.004**	0.28
SF-36, mean (SD)										
Physical functioning	19.69 (21.92)	18.63 (21.43)	1.566	0.118	0.06	18.09 (21.00)	15.91 (20.28)	1.362	0.176	0.13
Social functioning	46.35 (27.37)	40.69 (26.86)	5.035	**0.000**	0.20	41.40 (26.83)	35.89 (26.30)	2.148	0.034	0.21
Limitations physical	50.81 (41.97)	44.52 (41.54)	3.714	**0.000**	0.15	47.27 (42.21)	44.77 (42.58)	0.56	0.576	0.05
Limitations emotional	61.04 (39.91)	54.50 (42.11)	3.437	**0.001**	0.13	61.21 (39.50)	51.82 (43.68)	2.079	0.040	0.20
Mental health	52.36 (20.50)	46.46 (20.62)	6.681	**0.000**	0.26	52.98 (21.05)	46.22 (21.66)	3.138	**0.002**	0.30
Vitality	58.05 (20.48)	54.19 (20.17)	4.71	**0.000**	0.18	59.45 (21.34)	53.45 (20.82)	3.012	**0.003**	0.29
Pain	28.56 (25.62)	26.36 (25.01)	2.441	0.015	0.10	26.97 (27.24)	23.84 (23.84)	1.423	0.158	0.14
General health	44.42 (21.89)	42.74 (21.56)	2.355	0.019	0.09	41.59 (21.99)	41.14 (20.46)	0.237	0.813	0.02
MADRS, mean (SD)	15.88 (9.38)	11.76 (9.01)	9.708	**0.000**	0.43	15.85 (9.26)	10.14 (7.85)	4.822	**0.000**	0.51
BAS, mean (SD)	13.67 (6.57)	10.81 (6.84)	8.475	**0.000**	0.38	14.21 (7.27)	9.70 (6.21)	4.637	**0.000**	0.49

Notes: B = baseline, 6 mo = after 6 months posttreatment. Concerns patients with both baseline and 6-month data.

p value denotes the paired *t* test, and significant *p* values ($p < 0.01$) are printed in bold.

Difference scores denote the subtractions scores of the baseline level and after 6 months.

none of the groups showed a significant improvement of self-reported physical functioning (SF-36 scale).

Predictors for the Treatment Course of Symptoms (BSI Total)

The course of the BSI total score was defined by the BSI total difference score (BSI total at 6 months minus BSI total at baseline). For the total group of the anxiety-related disorders ($N = 470$; not in table), we found that the average BSI total difference score was −0.19, with a standard deviation of 0.71 (minimal difference score of −0.24 and maximum difference score of −0.13).

Table 5A (see Supplementary Material, Supplemental Digital Content 1, http://links.lww.com/JNMD/A165) displays the results of the hierarchical multiple linear regression analysis for the BSI total difference score.

When the effects of the pretreatment outcome BSI total score and sociodemographic variables were statistically controlled, we found five significant predictors for the course of the BSI difference score (predictors: $*p < 0.05$; $**p < 0.01$; $***p < 0.001$): comorbid somatoform disorder, total diagnoses (total comorbid disorders present besides the anxiety-related disorder), SF-36 physical functioning, SF-36 general health, and MADRS (explained variance by predictors: 0.100 or 10%).

Predictors for the Treatment Course of Functioning (SF-36 Physical Functioning)

The course of the SF-36 physical functioning score was examined by means of the SF-36 physical difference score (SF-36 physical at 6 months minus SF-36 physical at baseline). The average SF-36 difference score for the total group of anxiety-related disorders ($N = 470$, not in table) was −1.75, with a standard deviation of 18.22 (minimal difference score of −3.16 and maximum difference score of −0.34).

Table 5B (see Supplementary Material, Supplemental Digital Content 1, http://links.lww.com/JNMD/A165) displays the results of the hierarchical multiple linear regression analysis concerning the SF-36 physical functioning difference score. When the effects of the pretreatment outcome SF-36 physical functioning score and sociodemographic variables were statistically controlled, we found no significant predictors for the course of SF-36 physical functioning.

DISCUSSION

Our study compared course outcomes between four different anxiety-related disorders after 6 months of treatment. Below is a summary of our results, which are discussed in light of the available relevant research literature.

First, our baseline results show that the anxiety-related disorder groups differed significantly from each other on baseline sociodemographic

TABLE 3. Six-Month Treatment Course of Panic Disorder Group (n = 120) and Obsessive-Compulsive Disorder Group (n = 95)

Patient Characteristics	Panic Disorder B	Panic Disorder 6 mo	t	p	Effect Size (d)	Obsessive-Compulsive Disorder B	Obsessive-Compulsive Disorder 6 mo	t	p	Effect Size (d)
BSI, mean (SD)										
Somatization	0.94 (0.74)	0.76 (0.72)	3.069	**0.003**	0.28	0.58 (0.54)	0.63 (0.76)	−0.678	0.499	−0.07
Obsessive-compulsive	1.33 (0.92)	1.23 (0.98)	1.344	0.182	0.12	1.52 (1.01)	1.27 (0.97)	2.630	0.010	0.27
Interpersonal sensitivity	1.31 (1.02)	1.20 (1.13)	1.500	0.136	0.14	1.16 (1.01)	1.07 (0.97)	1.210	0.229	0.12
Depression	1.33 (1.08)	1.19 (1.09)	1.593	0.114	0.15	1.09 (0.95)	0.97 (0.96)	1.659	0.101	0.17
Anxiety	1.31 (0.92)	1.19 (0.93)	1.431	0.155	0.13	1.27 (0.94)	1.03 (0.96)	2.791	**0.006**	0.29
Hostility	0.68 (0.71)	0.79 (0.87)	−1.639	0.104	−0.15	0.64 (0.69)	0.55 (0.59)	1.414	0.161	0.15
Phobic anxiety	1.34 (0.95)	1.11 (0.98)	2.554	0.012	0.23	0.78 (0.77)	0.63 (0.77)	2.303	0.024	0.24
Paranoid ideation	0.87 (0.78)	0.88 (0.85)	−0.277	0.782	−0.03	0.74 (0.80)	0.64 (0.64)	1.440	0.153	0.15
Psychoticism	1.07 (0.90)	0.96 (0.90)	1.686	0.094	0.15	1.00 (0.85)	0.80 (0.83)	2.839	**0.006**	0.29
Total score	1.13 (0.72)	1.03 (0.77)	1.778	0.078	0.16	0.98 (0.69)	0.84 (0.69)	2.435	0.017	0.25
SF-36, mean (SD)										
Physical functioning	24.07 (23.14)	23.47 (21.46)	0.351	0.726	0.03	16.36 (19.85)	15.22 (19.67)	0.646	0.520	0.07
Social functioning	48.84 (27.47)	43.28 (26.78)	2.114	0.037	0.19	39.81 (27.17)	31.11 (25.91)	2.913	**0.005**	0.30
Limitations physical	53.78 (41.89)	49.16 (43.17)	1.213	0.227	0.11	45.38 (42.57)	31.25 (37.91)	2.906	**0.005**	0.30
Limitations emotional	60.22 (40.54)	53.50 (41.22)	1.552	0.123	0.14	57.61 (40.18)	43.12 (42.38)	2.703	**0.008**	0.28
Mental health	49.31 (21.24)	46.62 (20.58)	1.312	0.192	0.12	51.52 (20.44)	39.87 (20.47)	5.442	**0.000**	0.57
Vitality	58.36 (21.09)	55.21 (21.83)	1.707	0.090	0.16	52.67 (21.61)	47.72 (20.18)	2.353	0.021	0.25
Pain	31.84 (25.42)	28.94 (25.48)	1.432	0.155	0.13	27.05 (24.34)	23.55 (22.64)	1.574	0.119	0.16
General health	49.54 (20.39)	46.51 (20.14)	2.005	0.047	0.18	40.05 (21.30)	36.47 (21.73)	2.035	0.045	0.21
MADRS, mean (SD)	14.62 (9.48)	11.57 (8.73)	3.670	**0.000**	0.37	12.79 (8.97)	9.76 (9.04)	3.109	**0.003**	0.37
BAS, mean (SD)	14.07 (5.97)	11.03 (6.42)	4.844	**0.000**	0.49	11.26 (5.93)	9.23 (6.78)	2.734	**0.008**	0.33

Notes: B = baseline, 6 mo = after 6 months posttreatment. Concerns patients with both baseline and 6-month data.

p value denotes the paired t test, and significant p values ($p < 0.01$) are printed in bold.

Difference scores denote the subtractions scores of the baseline level and after 6 months.

and clinical characteristics, although differences were mostly small. These results are difficult to compare with those of other studies, which usually focused on characteristics of a total group of anxiety disorders. For example, anxiety-related disorders are generally more common in women than in men (*e.g.*, Bandelow and Michaelis, 2015; Farhane-Medina et al., 2022; Kessler et al., 1994; Kessler et al., 2005b; Pesce et al., 2015; Michael et al., 2007), which is confirmed in our results (for both total group and disorder groups). This sex difference can probably be explained by psychosocial and biological factors, although more research is needed on this (Farhane-Medina et al., 2022). Further, previous studies have primarily documented lower prevalence rates of anxiety disorders in minority groups (*e.g.*, Asnaani et al., 2010; Michael et al., 2007), which is again consistent with our results (for both total and disorder groups). Although more research is needed, some possible reasons have been suggested for these ethnic differences, for example, language/cultural differences in anxiety expression and/or in the conceptualization of anxiety symptoms in diagnostic instruments (Asnaani et al., 2010; Michael et al., 2007). In conclusion, it can be said that the present study extends prior research by providing additional insight into differences within specific anxiety-related disorders.

Second, overall treatment course of our anxiety-related disorder groups showed a rather modest improvement. In line with our expectations, only generalized anxiety disorder and posttraumatic stress disorder (but not panic or obsessive-compulsive disorders) showed a significant yet small improvement in self-rated psychopathology (BSI total). In contrast with these partially positive self-report course results, all four anxiety-related disorder groups significantly improved in clinician-rated psychopathology (MADRS and BAS). These mixed results are not uncommon in the literature; although self-reporting and observer-rated measures mostly concur, they can sometimes diverge markedly in anxiety-related disorders (Schat et al., 2017; Zimmerman et al., 2018). In line with our results, Schat et al. (2017) found that anxiety patients had a lower clinician-rated anxiety severity compared with self-rating. Possible explanations for this are, for example, random measurement error, different item content of self-rated and clinician-rated instruments, rater characteristics, or patients characteristics (*e.g.*, personality traits) (Schat et al., 2017).

Another striking result concerns the fact that none of our anxiety-related disorder groups, except posttraumatic stress disorder, improved on hostility (BSI), suggesting that hostility/anger is rather persistent. This corresponds to the majority of the literature, showing a potentially important relationship between most anxiety-related disorders and anger problems (*e.g.*, Hawkins and Cougle, 2011; Thompson and Schmidt, 2021). In line with our results, Hawkins and Cougle (2011) found that posttraumatic stress disorder, compared with other anxiety-related disorders, was the disorder that was least associated with anger. One explanation for why anxiety and anger frequently co-occur is that individuals with elevated levels of anxiety tend to be more vigilant toward perceived threat/stress (*e.g.*, Barlow et al., 2004; Thompson and Schmidt, 2021), which may lead to increased irritability (American Psychiatric Association, 2013; Thompson and Schmidt, 2021), hostility (Olatunji et al., 2010; Thompson and Schmidt, 2021), anger attacks (Fava et al., 1990; Thompson and Schmidt, 2021), indirect aggression (Mallott, 2012; Thompson and Schmidt, 2021), and direct aggression (Mallott, 2012; Thompson and Schmidt, 2021).

None of our anxiety-related disorder groups showed a significant improvement in self-reported SF-36 physical functioning. In line with this, none of the anxiety-related disorder groups showed a significant

TABLE 4. Six-Month Treatment Course of Posttraumatic Stress Disorder Group ($n = 144$)

Patient Characteristics	Posttraumatic Stress Disorder B	Posttraumatic-Stress Disorder 6 mo	*t*	*p*	Effect Size (*d*)
BSI, mean (SD)					
Somatization	1.14 (0.89)	0.93 (0.78)	2.740	**0.007**	0.23
Obsessive-compulsive	1.79 (1.03)	1.48 (0.95)	3.177	**0.002**	0.26
Interpersonal sensitivity	1.71 (1.16)	1.26 (1.00)	4.830	**0.000**	0.40
Depression	1.78 (1.11)	1.36 (1.07)	3.908	**0.000**	0.33
Anxiety	1.49 (1.02)	1.18 (0.90)	3.461	**0.001**	0.29
Hostility	1.12 (0.98)	0.84 (0.77)	3.818	**0.000**	0.32
Phobic anxiety	1.05 (0.90)	0.79 (0.84)	3.575	**0.000**	0.30
Paranoid ideation	1.46 (1.01)	1.17 (0.93)	3.682	**0.000**	0.31
Psychoticism	1.37 (0.92)	1.04 (0.86)	4.327	**0.000**	0.36
Total score	1.44 (0.84)	1.13 (0.75)	4.313	**0.000**	0.36
SF-36, mean (SD)					
Physical functioning	27.70 (25.88)	26.24 (24.94)	0.903	0.368	0.08
Social functioning	53.01 (26.09)	47.34 (25.08)	2.204	0.029	0.19
Limitations physical	63.48 (40.48)	58.87 (38.86)	1.271	0.206	0.11
Limitations emotional	69.50 (39.54)	62.41 (42.14)	1.652	0.101	0.14
Mental health	56.82 (20.30)	51.29 (19.13)	2.845	**0.005**	0.24
Vitality	64.22 (19.07)	59.43 (17.37)	2.599	0.010	0.22
Pain	38.14 (27.10)	36.64 (27.08)	0.678	0.499	0.06
General health	50.92 (21.27)	48.90 (21.09)	1.222	0.224	0.10
MADRS, mean (SD)	20.46 (9.09)	15.39 (9.02)	4.855	**0.000**	0.46
BAS, mean (SD)	15.13 (6.59)	12.70 (6.86)	2.963	**0.004**	0.28

Notes: B = baseline, 6 mo = after 6 months posttreatment. Concerns patients with both baseline and 6-month data.

p value denotes the paired *t* test, and significant *p* values ($p < 0.01$) are printed in bold.

Difference scores denote the subtractions scores of the baseline level and after 6 months.

improvement on the other somatically/physically oriented subscales—pain and general health. Our results are confirmed by previous studies, showing that an unfavorable clinical course of anxiety-related disorders is rather common (*e.g.*, Disabato et al., 2021; Hellström et al., 2021; Keller, 2006; Keller and Hanks, 1993; Ormel et al., 1993; Penninx et al., 2011; Pollack and Otto, 1997; Tiemens et al., 1996) and that patients with anxiety-related disorders responded less well to treatment (*e.g.*, Angst and Vollrath, 1991; Bruce et al., 2005; Fichter et al., 2010; Rhebergen et al., 2011; Yonkers et al., 2003). Possible explanations for the nonimproved physical functioning of our patients are, for example, that this requires additional specific interventions (*e.g.*, physical exercises, Imboden et al., 2022; Kandola et al., 2018; Machado et al., 2022; Vancampfort et al., 2022; Yu et al., 2022), or that our patients also had a complicating (chronic) physical illness (not measured by us), which is common in people with anxiety disorders (*e.g.*, Henning et al., 2018; Sharpe et al., 2022).

Third, we found five significant predictors for the treatment course of symptoms (BSI): comorbid somatoform disorder, total comorbid diagnoses, SF-36 physical functioning, SF-36 general health, and MADRS score. We found no sociodemographic predictors, which is consistent with review results showing that persistent anxiety was predicted primarily by clinical and psychological features and not by sociodemographic factors (Hovenkamp-Hermelink et al., 2021). In line with our results, several studies also found comorbidity to be a predictor of an unfavorable treatment course (Bruce et al., 2005; Van Beljouw et al., 2010). Finally, also in line with our results, previous studies on anxiety-related disorders found that a higher severity of baseline symptoms (Ronalds et al., 1997; Van Beljouw et al., 2010) and more physical impairment (*e.g.*, Scholten et al., 2013; Ten Have et al., 2020) were significant predictors of an unfavorable treatment course. In sum, our five predictors provide a consistent picture of an unfavorable prognosis for complicated anxiety patients characterized by comorbid physical and psychological complaints with impaired functioning at the beginning of treatment.

Our finding of comorbid somatoform disorder as a significant predictor for the treatment course of symptoms in anxiety-related disorders is not in line with the results of Batelaan et al. (2014) who found that severity, anxiety duration, and disability were able to better identify chronic course trajectories of anxiety-related disorders as compared with *DSM-IV* categories. However, several studies have shown an association between anxiety-related disorders and somatoform disorders (*e.g.*, Behm et al., 2021; De Waal et al., 2004; Lieb et al., 2007; Ma et al., 2021; Newby et al., 2017) or somatic diseases (*e.g.*, Henning et al., 2018; Ten Have et al., 2020). The most direct relationship between anxiety and somatization is probably reflected in the concept of health/illness anxiety, which can be influenced by personality traits (*e.g.*, Lee et al., 2015; Newby et al., 2017; Nikčević et al., 2021). The majority of studies indicate that anxiety-related disorders and health anxiety are associated with increased health care utilization across multiple care settings (*e.g.*, Horenstein and Heimberg, 2020).

In contrast to what we unexpected, we found no predictors of functional course (SF-36). Baseline symptom severity as a predictor of the treatment course of functioning seemed plausible; anxiety symptoms are often associated with functional distress and impairment (Craske et al., 2011). Iancu et al. (2014) found that worse functioning in anxiety-related disorders was predicted by their severity, use of psychological treatment, comorbid depressive disorders, and maladaptive personality traits. Perhaps our 6-month follow-up period was too short to analyze functional course predictors, nor were all relevant predictors available in our ROM data set.

Clinical Considerations and Future Research

In line with previous studies (*e.g.*, Hendriks et al., 2013), we found that various anxiety-related disorders had different treatment courses. In terms of staging, our sample fits the last stage or the "comorbid complicated stage" (comorbidity with other mental disorders; Bokma et al., 2020). When treating anxious patients with co-occurring depression, research has demonstrated that short-term changes in anxiety mediate changes in depression—the reverse is true for the long-term outcome period (Bomyea et al., 2015). Previous studies have also shown that anxiety-related disorders and the anxiety-mood disorders comorbidity are associated with more severe symptoms and more impaired functioning (*e.g.*, Hofmeijer-Sevink et al., 2012) and with more suicidality (Bentley et al., 2016; Sareen et al., 2005). The anxiety–anxiety disorders comorbidity could not be analyzed in this study and should be considered in future research. We further found that in almost all anxiety-related disorders no improvement was seen on the physical subscales (BSI and SF-36), which may have clinical implications. For instance, a previous study found that chronic obsessive-compulsive disorder is significantly different in symptoms and physical functioning to nonchronic obsessive-compulsive disorder, and it needs to be treated differently (Visser et al., 2014).

In addition, since hostility/anger did not decrease significantly in most anxiety-related disorders despite treatment, it seems important to specifically address hostility/anger (*e.g.*, Asberg, 2013; Hawkins and Cougle, 2011; Kuo et al., 2021; Thompson and Schmidt, 2021). This is all the more important because research suggests that both anxiety and anger are risk factors for serious physical health problems (Hawkins and Cougle, 2011; Roy-Byrne, 2015). Anxiety sensitivity treatment (Thompson and Schmidt, 2021; Zvolensky et al., 2006) or transdiagnostic treatments designed to target emotional dysregulation may be particularly helpful in treating these comorbid anxiety/anger profiles (Barlow et al., 2004).

Lastly, more research is necessary to see the long-term effects of anxiety treatments, specified for type and intensity, on both symptom remission and functional recovery—particularly with respect to persistent and treatment-resistant anxiety-related disorders (*e.g.*, Barton et al., 2014; Milrod et al., 2016; Patterson and Van Ameringen, 2016; Solbakken and Abbass, 2016). We also recommend further research concerning treatment compliance as it has been found that compliance was a major predictor of treatment course outcome in, for example, panic disorder (*e.g.*, Rubio and López-Ibor, 2007). In this context, Marker et al. (2020) demonstrated superior effects of motivational interviewing used as an adjunct to CBT. The therapeutic alliance has shown promise as a predictor of favorable therapy outcomes, and further research on mediators and moderators of the alliance-outcome relationship is important (*e.g.*, Buchholz and Abramowitz, 2020; Luong et al., 2020).

Strengths and Limitations

Strengths of our study include the naturalistic secondary mental health care sample of outpatients with different anxiety-related disorders, the use of both observer-rating and self-report measures, and the focus on both symptoms and functioning as treatment outcomes.

Our study also had limitations, such as the lack of disorder-specific measurements. However, Schawo et al. (2019) showed that generic instruments (*e.g.*, BSI) were equally suited, compared with disorder-specific instruments, to detect treatment change at group level for most anxiety-related disorders. We had no randomized control group, so it remains unclear whether the changes we found are the result of treatment, of regression to the mean, or of natural fluctuations in severity over time. Nevertheless, our findings regarding the fairly moderate improvements in symptoms and functioning in different anxiety disorders are largely consistent with the literature (*e.g.*, Bruce et al., 2005; Disabato et al., 2021; Fichter et al., 2010; Hellström et al., 2021; Penninx et al., 2011; Rhebergen et al., 2011). There were only four anxiety-related disorders with complete pretreatment to posttreatment data, and our patients were diagnosed according to the *DSM-IV-R*. The latter implies that no account was taken of the changes as listed in the *DSM-5* (American Psychiatric Association, 2013; Kupfer, 2015). We followed patients for a period of just 6 months posttreatment, which may have been too short to analyze the final outcome and its predictors, in particular with regard to physical functioning. However, our results do have clinical relevance, as Boer et al. (2019) demonstrated that self-assessed symptom severity at 2–6 months of treatment follow-up was a strong indicator for prolonged treatment course and chronicity. Another limitation was that we had no individual information about treatment content, frequency, or total duration. This limited our ability to focus on the outcome of specific treatments and to fully understand (non)significant symptom changes over time. Also, our analysis of course outcome predictors was limited to the predictors measured in this study. Given the low percentage of explained variance of the predictors found in this study, it is likely that there may also be other relevant course predictors (*e.g.*, co-occurring personality disorders [Vergés et al., 2014]; childhood trauma and attachment style [Kuzminskaite et al., 2021; Tibi et al., 2020]; neural predictors [Picó-Pérez et al., 2022; Santos et al., 2019; Vieira et al., 2022]). In addition, there were only two measuring points (pre/post), so there was no insight into pattern or speed of change during treatment. Finally, our participants were all treatment-seeking, which prevents the generalizability of our findings to non–treatment-seeking individuals.

CONCLUSIONS

Our results contribute to current knowledge regarding the clinical course of anxiety-related disorders in secondary mental health care. We showed that different anxiety-related disorders generally had a rather unfavorable 6-month treatment course for functional outcomes in particular. Furthermore, the number and type of comorbid diagnoses, observer-rated depression, as well as physical functioning and general health were significant predictors for symptom remission. Finally, our findings highlight the importance of reducing chronicity as well as some additional anxiety treatment topics such as physical complaints, hostility/anger, suicidal ideation, and comorbid depression or comorbid somatization disorder.

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DISCLOSURES

All authors have read and approved the submitted manuscript, as well as a summary of the contributions of each author. All authors have made substantive intellectual contribution to the development of the manuscript, and they agree to be accountable for all aspects of the manuscript (accuracy/integrity, conception/design, data acquisition/analysis/interpretation,/reporting, drafting/revising the manuscript, and final approval of the version to be published). Carlier was especially responsible for designing, data-stewardship, drafting/revising, and total supervision of the study/manuscript. Van der Elst was especially responsible for data acquisition/analysis/interpretation/reporting. De Jong and Van Vliet were especially responsible for drafting/revising the manuscript.

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The study was conducted according to current research standards. The Medical Ethical Committee of the Leiden University Medical Center approved the general study protocol regarding ROM. ROM is considered integral to the treatment process, so no written informed

consent is institutionally required. A comprehensive protocol (titled "Psychiatric Academic Registration Leiden database") was used, which safeguarded the anonymity of participants and ensured proper handling of the data. None of the participants objected to the anonymized use of their data for scientific purposes.

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