ORIGINAL ARTICLE

Longterm persistence and nonrecurrence of depression treatment in Germany: a four-year retrospective follow-up using linked claims data

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Abstract

Objectives: To measure persistence and nonrecurrence of depression treatment and investigate potential risk factors.

Methods: We retrospectively observed a closed cohort of insureds with new-onset depression treatment in 2007 and without most psychiatric comorbidity for 16 quarters (plus one to ascertain discontinuation). We linked inpatient/outpatient/drug-data per person and quarter. Person-quarters containing specified depression services were classified as depression-treatment-person-quarters (DTPQ). We defined *longterm-DTPQ-persistence* as 16 + 1 continuous DTPQ and *longterm-DTPQ-nonrecurrence* as 12 continuous quarters without DTPQ and used multivariate logistic regression to explore associations with these outcomes.

Results: Within first 16 quarters, 28,348 patients' first period (total time) persisted for a mean/median 5.4/3 (8.7/8) quarters. Fourteen percent had *longterm-DTPQ-persistence*, associated ($p < .05$) with baseline hospital (odds ratio, OR = 1.80), psychotherapy/specialist-interview and antidepressants (OR = 1.81), age (years, OR = 1.03), unemployment (OR = 1.21), retirement (OR = 1.31), and insured as a dependent (OR = 1.32). Thirty-four percent had *longterm-DTPQ-nonrecurrence*, associated with psychotherapy/specialist-interview (OR = 1.40), antidepressants (OR = 0.54), female sex (OR = 0.84), age (years, OR = 0.99), retirement (OR = 1.18), and insured as a dependent (OR = 0.88). Women differed for episodic and not chronic treatment.

Conclusion: Treatment measures compared to survey's symptoms measures. We suggest further research on "treatment-free-time." Antidepressants(-) and psychotherapy/specialist-interview(+) were significantly associated with *longterm-DTPQ-nonrecurrence*. This was presumably moderated by possible short-time/low-dosage antidepressants use(-) and selective therapy assignment(+). Sample selectivity limited data misclassification.

KEYWORDS

depressive disorder, longitudinal studies, psychotherapy, recurrence, risk factors

1 | INTRODUCTION

Depression has a high prevalence (Jacobi et al., 2014), often results in disability (Paykel, Brugha, & Fryers, 2005) and causes society substantial costs (Gustavsson et al., 2011). *Longterm persistence* (chronification) and *nonrecurrence* (stable recovery) are the worst and best "lifetime" outcomes of depression. We measure longterm

persistence and nonrecurrence of depression treatment and explore their risk factors.

Prospective follow-up studies that are representative and cover primary, secondary, and inpatient care for several years with close measurement intervals and good follow-up rates are seldom (Lee, 2003). We considered mostly studies listed in four systematic reviews (Gilchrist & Gunn, 2007; Hardeveld, Spijker, De Graaf, Nolen, &

Beekman, 2010; Steinert, Hofmann, Kruse, & Leichsenring, 2014a; van Weel-Baumgarten, Schers, van den Bosch, van den Hoogen, & Zitman, 2000). We searched for studies following patients for ≥ 4 years with ≥ 3 follow-up measurements and found clinical studies recruiting in primary care (Riihimäki, Vuorilehto, Melartin, & Isometsa, 2014), secondary care (Furukawa, Kitamura, & Takahashi, 2000; Holma, Holma, Melartin, Rytsala, & Isometsa, 2008; Kanai et al., 2003; Keller et al., 1992; Maj, Veltro, Pirozzi, Lobraccio, & Magliano, 1992; Mueller et al., 1999; Solomon et al., 1997), and tertiary care (Naz et al., 2007). One German survey followed inpatients for 3 years after discharge (Seemuller et al., 2014).

These and similar “clinical cohorts” provide landmark measures of depression persistence or recurrence but cannot avoid methodological shortcomings such as selectivity by setting, Bergson's bias, (differential) recall bias, Hawthorne effect, and attrition. Sample sizes ranged from $n = 87$ (Naz et al., 2007) to $n = 431$ (Keller et al., 1992). This limits detailed multivariate analysis, especially of infrequent explanatory variables (Lee, 2003). Associations of gender or further variables with depression persistence/recurrence were frequently not conclusive across studies (Hardeveld et al., 2010; Steinert et al., 2014a; van Weel-Baumgarten, Schers, et al., 2000).

Representative studies with a large sample, longterm follow-up, and close measurement are hardly feasible and expensive (Cochran & Chambers, 1965). We decided on a retrospective approach and discuss limitations of this (Hemkens, Contopoulos-Ioannidis, & Ioannidis, 2016). The Institute for Quality and Efficiency in Healthcare (IQWiG, 2013) and the BARMER GEK statutory health insurance (SHI) provided resources and claims data to analyse treatment patterns in Germany.

Our first objective was to analyse depression treatment in each quarter for 16 quarters and to measure

- the proportion of patients with continual treatment (longterm persistence);
- the proportion of patients who stop and never resume treatment (longterm nonrecurrence);
- the median/average time to first treatment discontinuation;
- the proportion of total time spent having treatment.

Our second objective was to identify variables associated with longterm persistence and nonrecurrence from baseline sociodemographic and depression treatment data.

2 | METHODS

2.1 | Design

We performed a retrospective follow-up study of a population-based closed cohort. We analysed patients with new-onset diagnosed depression treatment in 2007 and no previous diagnosis of depression in 2006. The study time ranged from 2007 to 2011. To estimate incidence of recurrence, we excluded persons who died, switched sickness funds, had no daily full insurance coverage, or moved abroad between 2006 and 2011 (Boenisch et al., 2011).

We analysed billed inpatient/outpatient-services related to a depression diagnosis (F32.x/F33.xICD-10), and outpatient antidepressant prescriptions (ATC-code N06Axx) per patient and quarter of the year (Sections 2.4 and 2.5). A patient's first quarter of observation was defined by the first depression-related service in 2007. We traced each patient for 16 quarters (plus one to ascertain discontinuation). We followed international (Benchimol et al., 2015; von Elm et al., 2007) and German (Swart et al., 2016) guidelines for reporting of observational studies.

2.2 | Data and subgroup for multivariate analysis

We analysed claims data from the single largest German SHI fund in 2010: the BARMER GEK. It then covered about 8.67 Mio insureds, $\sim 11\%$ of the German SHI population for ≥ 1 day (Grobe, Dörning, & Schwartz, 2012). In 2010, the BARMER GEK resulted out of the merger of BARMER and GEK. We used subsequently merged and anonymised data from 2006 to 2011.

Data on “insurance status” in the baseline year 2007—before the merger—were only available to us for persons then insured by the BARMER, but not for those from the smaller GEK. We used spatial data on population and psychotherapist density provided by the Federal Office for Building and Regional Planning (INKAR) for 2008, linking the data to a patient's municipality key in 2007.

We defined a *subgroup* of persons for whom premerger data on “insurance status” and a German municipality key were available. For this subgroup, we had complete and comprehensive baseline data. We used this subgroup for multivariate exploration of associations of baseline variables (Figure 1i, Table 1b, Table 3).

Physicians in Germany code outpatient diagnoses as “ruled out”, “asymptomatic”, “suspected”, and “confirmed”. We analysed solely outpatient (inpatient) treatment files holding specified “confirmed” (main discharge) diagnoses (Gerste & Roick, 2014; Kleine-Budde et al., 2013). The term “physician” includes medical/psychological psychotherapist.

2.3 | Study population

We included patients of any age with assured, newly diagnosed unipolar depression in 2007 (Townsend, Walkup, Crystal, & Olfson, 2012) according to a case definition (Gerste & Roick, 2014; IQWiG, 2013; Kleine-Budde et al., 2013; Spettell et al., 2003). We used diagnoses of “single depressive episode” (F32.0/1/2/8/9ICD-10) or “recurrent depression” (F33.0/1/2/8/9ICD-10) in 2007. We included patients if they had at least (case definition, Figure 1b)

- two outpatient diagnoses by two physicians within one quarter,
- two outpatient diagnoses within two different quarters, or
- one inpatient diagnosis.

To ensure *new-onset* depression treatment, we excluded patients with ≥ 1 preexisting outpatient or inpatient depression diagnosis (F32.x/F33.xICD-10) in 2006 (Figure 1c). We did not exclude patients with antidepressant prescriptions in 2006 (ATC-code N06Axx) who had no

Diag.: Diagnosis, diagnosis codes refer to ICD-10 German modification version 2009.

^a The insured population of the BARMER GEK is largely homogeneously distributed across all 16 German federal states. Its proportion of females slightly exceeds the population average.

^b F4x.x ICD-10: "Neurotic-, stress and somatoform disorders".

FIGURE 1 Selection of study population

coexisting depression diagnosis as these antidepressant prescriptions were possibly meant for other conditions (Melfi & Croghan, 1999). We did not exclude patients with additional other depression diagnoses of F31.x/F32.3/F33.3/F32.4/F33.4/F34.x ICD-10.

From the 2007 data, we excluded all patients with any other psychiatric diagnosis of F0/F1/F2/F4/F5/F6/F7/F8/F9 ICD-10 (Figure 1d). Beyond 2007, we excluded all patients newly diagnosed with F0/F1/F2/F5/F6/F7/F8/F9 ICD-10 (Figure 1f). We did not exclude newly diagnosed "neurotic stress and somatoform disorders" (F4x.x ICD-10), a diagnostic group that frequently overlaps with depression. We regarded it as "concomitant symptoms" of previously diagnosed depression (Silverstone & von Studnitz, 2003; Wiegand, Sievers, Schillinger, & Godemann, 2016).

We excluded diagnosed psychiatric comorbidity in 2007 and beyond to exclusively analyse depression disease and avoid bias by psychiatric comorbidity and possible misclassification of outpatient psychiatric services (Section 2.4).

2.4 | Identifying and classifying depression treatment

For every patient and every quarter of observation, we classified all treatment files into five categories of depression treatment: one for hospital, three for outpatient physician, and one for antidepressant services (Figure 2). We built these categories in three steps: We extracted any treatment file related to depression disease from 2007 to 2011 (Figure 2a), sorted treatment files per person and quarter (Figure 2b), grouped three categories for outpatient physician treatment (Figure 2c).

Three outpatient categories were necessary because a quarter with a confirmed outpatient physician depression diagnosis does not necessarily reflect ongoing treatment of depression. The diagnosis might not be valid (Mitchell, Vaze, & Rao, 2009). The diagnosis might be noted as "secondary" and not reflect de facto treatment of acute symptoms (Giersiepen, Pohlabeln, Egidi, & Pigeot, 2007).

However, one can validate a diagnosis by the same diagnosis in preceding or subsequent quarters. We used this for our case definition

PQ: Person quarter; DTPQ: Depression treatment person quarter;

^a Closed inpatient or day care hospital stays covering at least one day of a corresponding quarter;

^b Billed per quarter and physician by associations of statutory health insurance physicians;

^c Purchased prescriptions sorted by prescription date as this reflects the doctor's visit and best drug data validity;

d3/d4/d12/d14: Solely outpatient psychotherapy service codes by =1 physician or medical/psychological psychotherapist;

d1/d2/d11/d13: Outpatient psychotherapy AND other service codes by ≥1 physician or medical/psychological psychotherapist.

FIGURE 2 Classifying categories (a-c) and combinations (d1-d19) of depression treatment (study population, 16 quarters)

(Section 2.3, Figure 1b). A diagnosis and possibly depression treatment can also be validated by confirming outpatient services delivered in the same quarter (Schubert, Ihle, & Koster, 2010). We therefore built three categories of outpatient services to confirm or reject treatment of possible symptomatic depression (Figure 2c,d):

- "Psychotherapy or specialist interview" (PT/SI) comprised service codes marking a psychotherapy session or neurological/psychiatric/medical-specialist interventions ≥10 min.
- "Other services" covered, for example, anamnesis; tests; training procedures; electroencephalogram, mostly provided by medical specialists, or psychotherapy report; probatory session; and urgent home visit provided by general practitioner, specialist, or psychotherapist.
- "No other services" defined minimum observed outpatient physician "treatment" by absence of any specified depression-related service code and only one physician noting the diagnosis.

TABLE 1 Baseline patient characteristics

	(a) Study population (N = 28,348)		(b) Subgroup (N = 23,229)	
(c) Enrolment data ^a				
Mean age (Standard Deviation)	48.9	(15.1)	49.8	(15.1)
	<i>n</i>	(%)	<i>n</i>	(%)
Sex female	22,930	(80.9)	19,274	(83.0)
Insurance status				
Employed	n.a.	n.a.	12,732	(54.8)
Unemployed	n.a.	n.a.	2,032	(8.7)
Retired	n.a.	n.a.	6,078	(26.2)
Insured as a dependent	n.a.	n.a.	2,387	(10.3)
Residency in East German States	3,561	(12.6)	3,065	(13.2)
(d) Spatial data ^b				
Urban area	19,658	(69.3)	16,225	(69.8)
Rural area	8,509	(30.0)	7,004	(30.2)
Number of psychotherapists per municipality				
0-9 ^c	4,744	(16.7)	4,016	(17.3)
10-23	13,734	(48.4)	11,166	(48.1)
≥ 24 ^d	9,689	(34.2)	8,047	(34.6)
Without German municipality key	181	(0.6)	n.a	n.a.
(e) Diagnosis and utilisation data				
Depression diagnosis ^e				
Unspecified/atypical	13,847	(48.8)	11,358	(48.9)
Mild	2,101	(7.4)	1,729	(7.4)
Moderate	7,934	(28.0)	6,490	(27.9)
Severe	4,466	(15.8)	3,652	(15.7)
Diagnosis of recurrent depression ^f	6,381	(22.5)	5,223	(22.5)
Baseline depression treatment category ^g				
Hospital	1,170	(4.1)	924	(4.0)
Psychotherapy/specialist-interview and antidepressants	5,599	(19.8)	4,637	(20.0)
Psychotherapy/specialist-interview Antidepressants	4,347	(15.3)	3,595	(15.5)
Other	6,948	(24.5)	5,613	(24.2)
Other	10,284	(36.3)	8,460	(36.4)
Calendrical quarter of first new-onset depression treatment ^h				
2007quarter1	14,184	(50.0)	11,544	(49.7)
2007quarter2	7,412	(26.1)	6,087	(26.2)
2007quarter3	5,627	(19.8)	4,672	(20.1)
2007quarter4	1,125	(4.0)	926	(4.0)

^a Generally longest continuous insurance status in 2007 (if ≥ 1 period of unemployment in 2007 then "unemployed");

^b Year 2008 spatial data, linked by municipality key of longest continuous insurance status in 2007. Year 2007 data not available. No indication of relevant change 2007 to 2008. Urban includes "urban" and "semi-urban."

^c First quartile and ^d fourth quartile among 414 German municipalities in 2008;

^e Highest level within quarter1-4; ^f ≥ 1 diagnosis of recurrence F33.x ICD-10 within quarter 1-4;

^g Most intense treatment category within quarter 1-2;

^h Case definition criterion "two outpatient diagnoses within two *different* quarters" (section 2.3) reduced the number of eligible patients per quarter: 2007quarter1 covered nine, 2007quarter2 covered four, 2007quarter3 covered one, 2007quarter4 covered zero possible combinations of quarters - e.g. 2007quarter1 + 2007quarter3 - to fulfil ≥ 2 different quarters with outpatient diagnosis. n.a.: Not applicable due to data inavailability or exclusion.

German physician associations use a fee-for-service system and a comprehensive list of single service codes to distribute SHI payments. To analyse treatment and costs related to depression disease, the

Institute for Quality and Efficiency in Health Care specified a sample list of service codes for a cost-effectiveness report on antidepressants (IQWiG, 2013). Service codes were extracted for a trial sample solely

diagnosed with depression, ranked by frequency per physician group, and independently reviewed by physician/economist. We used this list for classification. A senior medical specialist further deleted a few service codes ambiguously signalling low-threshold maintenance therapy. Service codes (see Supporting Information) were tested for annual consistency using frequency analysis.

Physician and SHI Association's data transfer agreements limit *diagnosis validation in the same quarter* (Zeidler et al., 2013): Diagnosis data are available by quarter only, whereas single services data are available by date of delivery. A psychiatric service cannot exclusively be linked to a depression diagnosis, for example, if bulimia was diagnosed in the same quarter and likewise indicates this service. To avoid possible misclassification, we excluded patients with concurrent psychiatric diagnoses (Section 2.3, Figure 1d,f).

2.5 | Tracing the course of depression treatment

In any quarter, a person could have an arbitrary combination of classified five categories of depression treatment (Figure 2d1–d20). Using these combinations, we defined depression-treatment-person-quarters (DTPQ). A DTPQ defines a *minimum combination* of depression treatment categories. A DTPQ was meant to indicate treatment of possibly symptomatic depression.

A DTPQ indicating *continuation or recurrence* of treatment had to cover at least one physician visit with a depression diagnosis and depression-related services (Figure 2d1–d16). Remaining categories (Figure 2d17–d19) did not qualify. We regarded them as maintenance therapy and prone to possible misclassification.

The end of a row of consecutive DTPQ (Figure 2d1–d16) was marked by one quarter without (Figure 2d17–d20). We assumed *recurrence* of treatment if a patient had a DTPQ (Figure 2d1–d16)

after at least one quarter without (≥ 13 weeks). Surveys similarly defined “ ≥ 8 weeks without symptoms” as full remission/recovery (Figure 3).

To mark the *very first new-onset* DTPQ in 2007, any combination of depression treatment categories sufficed (Figure 2d1–d19), including sole antidepressant prescriptions and/or depression diagnoses without depression-related services (Figure 2d17–d19). We did so to sensitively capture the first symptoms presentation to a physician (AWMF, 2015; Hornbrook, Hurtado, & Johnson, 1985; Schneeweiss et al., 2010).

We followed methodological considerations on data-based episode construction (Hornbrook et al., 1985; Kessler, Steinwachs, & Hankin, 1980; Wingert, Kralewski, Lindquist, & Knutson, 1995).

2.6 | Defining outcomes

Longterm-DTPQ-persistence gives the number of patients with 16 + 1 consecutive quarters of DTPQ-continuation as opposed to patients with 16 or less quarters.

Longterm-DTPQ-nonrecurrence gives the number of patients without DTPQ (Figure 2d1–d16) in quarters five to 16 for a subgroup of patients with at most four consecutive quarters of DTPQ in the beginning of observation.

Time-to-first-DTPQ-discontinuation gives the number of consecutive DTPQ, beginning with the first new-onset DTPQ, within 16 quarters.

Total-time-spent-with-DTPQ gives the possible intermittent number of DTPQ within first 16 quarters.

2.7 | Baseline patient characteristics

We classified each patient's baseline level of *severe* (F32.2/F33.2), *moderate* (F32.1/F33.1), *mild* (F32.0/F33.0), or *other* (F32.8/F33.8/

TABLE 2 Univariate analysis of longterm depression treatment (study population)

Group	(a) Time-to-first-DTPQ- discontinuation within 16 quarters (quarters)						(b) Total-time-spent- with-DTPQ within 16 quarters (quarters)						(c) Longterm- DTPQ-persistence for 16+1 quarters (proportion of patients)		(d) Longterm- DTPQ-nonrecurrence for ≥ 12 quarters (proportion of patients)		
	N	Mean (SD)	P25	P50	P75		Mean (SD)	P25	P50	P75	%		n	%	N	n	%
Total	28,348	5.44 (5.34)	2	3	8		8.68 (5.24)	3	8	14	54.3		3,780		17,970	6,131	34.1
Male	5,418	5.17 (5.13)	2	3	7	n.s.	8.26 (5.23)	3	7	14	51.6		649	12.0	3,566	1,380	38.7
Female	22,930	5.50 (5.39)	2	3	8		8.78 (5.24)	3	8	14	54.9		3,221	14.0	14,404	4,751	33.0
Age < 65	23,647	5.21 (5.13)	2	3	7	b	8.45 (5.17)	3	8	14	52.8		2,845	12.0	-	-	-
Age ≥ 65	4,701	6.55 (6.21)	2	3	14		9.82 (5.48)	4	11	15	61.4		1,025	21.8	-	-	-
Baseline depression treatment category																	
Hospital	1,170	7.04 (5.85)	2	4	14		9.91 (5.33)	5	11	15	61.9		255	21.8	587	188	32.0
PT/SI and AD	5,599	6.68 (5.63)	2	4	12		9.62 (5.22)	5	10	15	60.1		1,057	18.9	2,907	974	33.5
PT/SI	4,347	5.40 (4.75)	2	3	7	c	7.53 (4.95)	3	6	12	47.1		366	8.4	2,579	1,234	47.8
AD	6,948	5.18 (5.58)	1	2	7		9.56 (5.19)	4	10	15	59.8		1,051	15.1	4,660	1,100	23.6
Other	10,284	4.77 (5.04)	1	2	6		7.92 (5.19)	3	7	13	49.5		1,141	11.10	7,237	2,635	36.4

PT/SI: Psychotherapy or specialist interview; AD: Antidepressant prescriptions; P25/P50/P75: Percentiles of distribution; P50: Median; - Not available due to timely limited data access;

n.s. Difference not significant, ^b Difference significant, Wilcoxon test, $p < 0.05$;

^c Pairwise differences significant ($p < 0.05/10$), except: "Hospital" vs. "PT/SI and AD" ($p = 0.179$), Wilcoxon test and Bonferroni correction for global hypothesis on "depression treatment category";

^d Pairwise differences significant ($p < 0.05/10$), except: "Hospital" vs. "PT/SI and AD" ($p = 0.083$), "Hospital" vs. "AD" ($p = 0.007$), "PT/SI and AD" vs. "AD" ($p = 0.109$), Wilcoxon test, Bonferroni corr.;

^e Group difference significant for $p < 0.05$, χ^2 df1;

^f Category differences significant for $p < 0.001$, χ^2 df4.

TABLE 3 Logistic regression models for longterm-DTPQ-persistence/nonrecurrence (subgroup)

Explanatory variables	(a) Outcome variable longterm-DTPQ-persistence (<i>N</i> = 23,229)			(b) Outcome variable longterm-DTPQ-nonrecurrence (<i>N</i> = 14,656 with first DTPQ- discontinuation in q2-q5)		
	0: ≤16 DTPQ (<i>n</i> = 19,988, 86.0%)			0: ≥1 DTPQ in q5-q16 (<i>n</i> = 9,684, 66.1%)		
	1: 16+1 DTPQ (<i>n</i> = 3,241, 14.0%)			1: 0 DTPQ in q5-q16 (<i>n</i> = 4,972, 33.9%)		
	Odds ratio	95% CI Wald	<i>p</i>	Odds ratio	95% CI Wald	<i>p</i>
Age (years)	1.033	(1.029 - 1.037)	<.001	0.988	(0.985 - 0.991)	<.001
Sex female	1.080	(0.971 - 1.201)	.157	0.836	(0.763 - 0.915)	<.001
Insurance status						
Employed (ref.)						
Unemployed	1.208	(1.043 - 1.400)	.012	0.992	(0.875 - 1.124)	.894
Retired	1.311	(1.172 - 1.467)	<.001	1.175	(1.052 - 1.311)	.004
Insured as a dependent	1.323	(1.158 - 1.513)	<.001	0.879	(0.783 - 0.986)	.028
Residency in						
West German states (ref.)						
East German states	1.176	(1.041 - 1.327)	.009	0.967	(0.861 - 1.086)	.569
Residency in						
Urban area (ref.)						
Rural area	1.103	(0.996 - 1.221)	.060	0.940	(0.854 - 1.035)	.208
Number of Psychotherapists per municipality						
0-9	0.844	(0.743 - 0.959)	.009	1.026	(0.912 - 1.154)	.668
10-23 (ref.)						
≥24	0.951	(0.869 - 1.041)	.274	0.951	(0.876 - 1.032)	.225
Depression diagnosis ^a						
Unspecified/atypical (ref.)						
Mild	0.708	(0.591 - 0.848)	<.001	1.148	(1.003 - 1.315)	.046
Moderate	0.994	(0.896 - 1.103)	.916	0.957	(0.873 - 1.050)	.351
Severe	1.313	(1.169 - 1.475)	<.001	0.848	(0.751 - 0.958)	.008
Recurrent depression ^b	1.701	(1.557 - 1.860)	<.001	0.717	(0.650 - 0.791)	<.001
Baseline depression treatment category ^c						
Hospital	1.797	(1.456 - 2.218)	<.001	0.940	(0.739 - 1.195)	.612
PT/SI and AD	1.814	(1.609 - 2.046)	<.001	1.050	(0.925 - 1.191)	.452
PT/SI	1.011	(0.884 - 1.157)	.869	1.398	(1.253 - 1.560)	<.001
AD	1.071	(0.971 - 1.182)	.171	0.541	(0.493 - 0.593)	<.001
Other (ref.)						
Quarter of first new-onset depression treatment						
2007 quarter 1 (ref.)						
2007 quarter 2	0.721	(0.654 - 0.795)	<.001	1.261	(1.160 - 1.371)	<.001
2007 quarter 3	0.841	(0.758 - 0.933)	.001	1.628	(1.484 - 1.785)	<.001
2007 quarter 4	0.850	(0.691 - 1.047)	.126	1.881	(1.567 - 2.257)	<.001

Ref.: reference group; DTPQ: Depression treatment person quarter; q: Quarter;

PT/SI: Psychotherapy or specialist interview;

AD: Antidepressant prescriptions; Model (a): *N* = 23,229, Mc-Fadden *R*² = 0.101, Hosmer-Lemeshow test: χ^2 = 22.090 (8 df), *p* = 0.005; Model (b): *N* = 14,656, Mc-Fadden *R*² = 0.065, Hosmer-Lemeshow test: χ^2 = 7.998 (8df), *p* = 0.434;^aHighest level within quarter 1-4; ^b≥1 diagnosis of recurrence F33.x ICD-10 within quarter 1-4;^cMost intense treatment category in quarter 1-2.

F32.9/F33.9) depression and recurrence (F33.x) by the most severe outpatient/inpatient diagnosis in the first new-onset DTPQ and three subsequent quarters (Table 1e). We chose four quarters to obtain a sustainable assessment of maximum severity (Kleine-Budde et al., 2013).

We hierarchically assigned five categories of *baseline treatment*: "hospital" treatment, "psychotherapy/specialist-interview and antidepressants," "psychotherapy/specialist-interview," "antidepressants," and "other" services (Table 1e). For this, we assigned each patient's *most intense* category of depression treatment (Section 2.4, Figure 2

FIGURE 3 Comparison of survey results

d) in the first new-onset DTPQ and one subsequent quarter (Boenisch et al., 2011; Heggstad, Lilleeng, & Ruud, 2011). We used two quarters as solely the first DTPQ might not adequately reflect subsequent transfers to specialised care (Gerste & Roick, 2014).

2.8 | Statistical analysis

We used Wilcoxon rank-sum tests to assess mean differences in *time-to-first-DTPQ-discontinuation* and *total-time-spent-with-DTPQ*. We assumed a full 3 months of observation time per quarter to compare results reported per month.

We used logistic regression to identify variables associated with *longterm-DTPQ-persistence* or *longterm-DTPQ-nonrecurrence*. We built a model using depression disease characteristics and sociodemographic variables as available in German claims data. Previous multivariate models based on German claims data explored associations with depression outcomes (Bramesfeld, Grobe, & Schwartz, 2010; Kleine-Budde et al., 2013; Wagner et al., 2016). We selected a comprehensive list of explanatory variables from these models and other models using survey data (Colman et al., 2011; Dowrick et al., 2011; Meyers et al., 2002; Viinamäki et al., 2006). To explore associations, we used the same set of explanatory variables for both outcomes.

We controlled for the calendrical first new-onset DTPQ as this variable is subject to seasonality and represents a "sampling weight"

reflecting selection bias induced by the cross-sectional year 2007 depression case definition (Höfler, Lieb, & Wittchen, 2007; Section 2.3).

The case definition criterion "two outpatient diagnoses within two different quarters" reduced the number of patients eligible per calendrical quarter in 2007 (Table 1e). This "skewness" reflects two factors associated with outcomes: First, patients selected in 2007quarter4 could only meet the criteria "one inpatient diagnosis" or "two outpatient diagnoses by two physicians within one quarter." They had more intense treatment than many patients selected in 2007quarter1 where just one physician diagnosis—validated later on—sufficed. Second, 2007quarter1 comprises the most "quarter-combinations" permitting a gap for physician diagnosis validation and thus the highest inherent probability for *early DTPQ-discontinuation* defined by a one-quarter gap.

Analysis was performed with SAS Version 9.2. Results were considered statistically significant for p values < .05.

3 | RESULTS

3.1 | Study population

We identified 28,348 newly diagnosed patients; 80.9% were female (Table 1c). Mean age at baseline was 48.9 years (SD 15.1, range 8–

98); 16.6% of patients were ≥ 65 years (Table 1, Table 2 calculation); 48.8% of patients were diagnosed solely with “unspecified/atypical” depression (F32.8/F33.8/F32.9/F33.9). Recurrent depression was diagnosed in 22.5% of patients (Table 1e).

The subgroup for multivariate analysis had more females (83.0% vs. 80.9%) and a higher mean age (49.8 vs. 48.9). There was no relevant difference in depression disease-related characteristics (Table 1a,b), *longterm-DTPQ-persistence*, and *longterm-DTPQ-nonrecurrence* (Table 2c,d, Table 3).

3.2 | Longterm-DTPQ-persistence and associated variables

Of identified patients, 13.7% had *longterm-DTPQ-persistence* for 16 + 1 quarters (Study population, Table 2c). Our multivariate model showed the following (subgroup, Table 3a, $p < .001$ where not stated otherwise):

The likelihood of *longterm-DTPQ-persistence* increased per year of age (+3.3%), and for

- patients with a baseline period of unemployment (+20.8%, $p = .012$, reference group “employed”),
- retirees (+31.1%, reference group “employed”),
- patients insured as a dependent (+32.3%, reference group “employed”),
- residents in East Germany (+17.6%, $p = .009$),
- a rural area (+10.3%, $p = .060$),
- patients with baseline treatment category “hospital” (+79.7%, reference group “other” services),
- patients with baseline treatment category “psychotherapy/specialist-interview and antidepressants” (+81.4%, reference group “other” services).

The likelihood of *longterm-DTPQ-persistence* decreased for

- areas with a low number of psychotherapists (−15.6%, $p = .009$),
- patients diagnosed with mild depression (−29.2%, reference group unspecified/atypical depression).

3.3 | Longterm-DTPQ-nonrecurrence and associated variables

Among 17,970 patients with up to four consecutive DTPQ at the beginning of observation, 34.1% had *longterm-DTPQ-nonrecurrence* (Study population, Table 2d). Our multivariate model showed the following (Subgroup, Table 3b, $p < .001$ where not stated otherwise):

The likelihood of *longterm-DTPQ-nonrecurrence* increased for

- retirees (+17.5%, $p = .004$, reference group “employed”),
- patients diagnosed with mild depression (+14.8%, $p = .046$, reference group unspecified/atypical depression),
- patients with baseline “psychotherapy/specialist-interview” (+39.8%, reference group “other” services).

The likelihood of *longterm-DTPQ-nonrecurrence* decreased per year of age (−1.2%), and for

- females (−16.4%),
- patients insured as a dependent (−12.1%, $p = .028$, reference group “employed”),
- patients with baseline treatment category “antidepressants” (−45.9%, reference group “other” services).

3.4 | Time-to-first-DTPQ-discontinuation

Median (mean) *time-to-first-DTPQ-discontinuation* was 3 quarters/~9 months (5.4 quarters/~16.3 months) within 16 quarters of follow-up (Table 2a). Following a bimodal distribution (Supporting Information), 63% of patients ($n = 17,970$, Table 2d, Figure 3) discontinued within year one, and 13.7% never discontinued within 16 + 1 quarters (Table 2c). On average, patients aged ≥ 65 years took about one quarter longer to DTPQ-discontinuation. We found no significant gender difference.

3.5 | Total-time-spent-with-DTPQ

Within 16 quarters, patients spent, on average, 54.3%/8.7 quarters/~26.0 months with defined depression treatment (Table 2b, Figure 2 d1-d16, Section 2.5). Patients aged ≥ 65 years spent more total-time-with-DTPQ (61.4%). Males spent less total-time-with-DTPQ (51.6%).

4 | DISCUSSION

We retrospectively traced 4 years of utilisation data. Fourteen percent (34%) of identified patients had *longterm-DTPQ-persistence* (*longterm-DTPQ-nonrecurrence*). This was comparable to depression symptom measures reported by prospective surveys.

To check plausibility of *longterm-DTPQ-persistence*, we selected four studies (Holma et al., 2008; Keller et al., 1992; Riihimäki et al., 2014; Solomon et al., 1997), best possibly matching follow-up-time, using *close follow-up measurement at least after month 6/18/60*, and *Longitudinal-Internal-Follow-up-Evaluation-Methodology* (Keller et al., 1987) for unipolar depression ($n > 100$) *treated* at baseline (Dintsios & Wagner, 2017; Figure 3). For *longterm-DTPQ-(non)-recurrence*, we selected three studies (Holma et al., 2008; Kanai et al., 2003; Kennedy & Paykel, 2004) that closely fitted these criteria.

4.1 | Treatment measures versus symptom measures

Surveys differently measured “discontinuation of depression symptoms.” The Finnish surveys (Holma et al., 2008; Riihimäki et al., 2014) defined “absence of any depression symptoms” (full-remission-definition). The U.S. surveys (Keller et al., 1992; Solomon et al., 1997) defined “absence of major depression tolerating residual symptoms” (tolerant-recovery-definition). It takes longer to reach full-remission-definition than tolerant-recovery-definition. This difference matters in comparisons.

Fourteen percent of patients had *longterm-DTPQ-persistence*. Surveys reported Kaplan–Meier-estimators of 27% (Riihimäki et al., 2014), 13% (Holma et al., 2008), 13% (Keller et al., 1992), and 9% (Solomon et al., 1997) of patients without symptoms discontinuation within 4 years (Figure 3). The 27% reported by Riihimäki et al. (2014) may result from their sample containing many longterm-ill or recurrent patients. Remaining proportions compared well. They seemingly demonstrate longterm convergence of chronic patients (Steinert et al., 2014a). This rate seems low as depressive illnesses are longterm disorders.

We measured three quarters (~9 months) median *time-to-first-DTPQ-discontinuation* within 4 years. This compared to Kaplan–Meier-estimation of median 20 (Riihimäki et al., 2014), 11 (Holma et al., 2008), 6 (Keller et al., 1992), and ~5 months (second episode; Solomon et al., 1997) until defined symptoms discontinuation within 5 years (10 years; Solomon et al., 1997).

Consistent with differing definitions of discontinuation, *time-to-first-discontinuation* and *longterm persistence* were highest for the Finnish studies (full-remission-definition) followed by our study (DTPQ), and lowest for the U.S. studies (tolerant-recovery-definition).

We found 34.1% of patients with *longterm-DTPQ-nonrecurrence* within 3 years. Surveys estimated higher proportions of patients with symptoms-nonrecurrence (taken from Kaplan–Meier curves):

- 40%, Finland, nonrecurrence of “major-depressive-episode,” 4 years (Holma et al., 2008);
- 41%, England, nonrecurrence of “major-depressive-episode,” 3 years (Kennedy & Paykel, 2004);
- 42%, Japan, nonrecurrence of “subthreshold depression,” 4 years, $n = 82$, 20 lost to follow-up (Kanai et al., 2003).

A DTPQ (Figure 2d1–d16) assumingly recurs more frequently than a full “major-depressive-episode.” A differing outcome definition might explain differing results. Kanai et al. (2003) measured “subthreshold depression.” Their results should compare better, but did not. Many censored observations might explain higher Kaplan–Meier-Estimators when compared to a retrospective closed cohort.

Patient's *total-time-spent-with-DTPQ* covered 54% of total observation time within 4 years. Similarly, patients spent “1%” and “20%” (Holma et al., 2008), or “24%” and “34%” (Riihimäki et al., 2014) of their total observed person-time in “partial remission” and “major-depressive-episode” within 5 years.

Inversely, patients had 46% *total-time-spent-without-DTPQ*. This compared to 49% (Holma et al., 2008) and 42% (Riihimäki et al., 2014) of time-spent-in-full-remission. DTPQ-classification seemingly covers any person-time with “partial remission” and “major-depressive-episode,” but nothing beyond “full remission.”

Differences in outcomes are mainly explained by differing definitions for measuring depression symptoms. For raw plausibility comparison, we assume negligibility of regional differences (Wittchen et al., 2011) and subordination of sampling/design differences. Our sample underrepresented low-threshold outpatient care (Section 4.4.4). This might facilitate comparability of respectively selective samples (Figure 3).

We largely excluded diagnosed existing and upcoming psychiatric comorbidity (Figure 1d,f). Surveys mostly excluded some relevant existing psychiatric comorbidity (Figure 3). Certain comorbidities possibly heterogeneously correlate with depression treatment or symptoms (Gijzen et al., 2001; Wagner et al., 2016). We found good outcome comparability, despite comorbidity sampling differences. Heterogeneous effects of psychiatric comorbidity possibly might “somehow even out.”

4.2 | Depression severity, sociodemographics, and longterm outcomes

Diagnosed unspecified/atypical depression showed a higher likelihood for longterm-DTPQ-persistence/recurrence than mild depression (Table 3a,b). Mostly general practitioners code unspecified/atypical depression (Wagner et al., 2016) for uncertain cases requiring watch-and-wait (Boenisch et al., 2011). Uncertain cases persist/recur more often than specified mild ones. This seems plausible.

Women did not differ from men in the duration/chronification of ongoing treatment. Consistent with cited studies, female gender was not significantly associated with longterm-DTPQ-persistence (Beekman et al., 2001; Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993) or time-to-first-DTPQ-discontinuation (Simpson, Nee, & Endicott, 1997).

However, women had more future periods of treatment. Female gender was associated with increased longterm-DTPQ-recurrence. Likewise, Ernst and Angst (1992) reported more recurrence of symptoms below major-depressive-episode, but not for specific DSM-III-R-criteria. Mueller et al. (1999) reported more women with recurring “psychiatric-status-rating level 1–6” but not with full major-depressive-episode. More recurrence of symptoms below major-depressive-episode confirmed more recurrence of assumingly “low-threshold” treatment.

Accordingly, women had more total-time-spent-with-DTPQ. Studies confirm this (Bracke, 2000; Winokur, Coryell, Keller, Endicott, & Akiskal, 1993). More future “low-threshold” treatment might not specifically relate to depression disease. Women in Germany generally have more drug prescriptions (Stock, Stollenwerk, Redaelli, Civello, & Lauterbach, 2008) and physician visits (Gerste & Günster, 2014).

Older age consistently showed a strong “deteriorating” association for all outcomes (van Weel-Baumgarten, Schers, et al., 2000). Regionally low psychotherapist-density was significantly associated with decreased longterm-DTPQ-persistence. Supply shortage could possibly influence shorter treatment. However, low psychotherapist-density could equally indicate a “healthy” area (Jacobi et al., 2016).

4.3 | Baseline treatment and longterm outcomes

Baseline treatment in “hospital” had a significant association with considerably increased longterm-DTPQ-persistence of *ongoing* treatment. Keller et al. (1984) confirmed this. “Hospital” was not significantly associated with *future* longterm-DTPQ-nonrecurrence. We found no comparable longitudinal evidence for verification.

Intense “psychotherapy/specialist-interview and antidepressants” treatment had a significant association with considerably increased

chronification of *ongoing* treatment but not with recurrence of *future* treatment. The German guideline recommends combination therapy for acute severe episodes (AWMF, 2015). Zobel et al. (2011) found more patients on *controlled* combination therapy with sustained remission in a 5-year randomised controlled trial (RCT) of inpatients. We found no such association in a population sample for *noncontrolled* combination treatment.

Baseline treatment reflects administered combination therapy by one physician but also patients who possibly successively visit more than one physician and possibly successively receive psychotherapist/specialist-interview and antidepressants. Rucci et al. (2011) reported more relapses within 6 months in patients requiring (subsequent) combination treatment to achieve remission. Some successive treatment “augmentation” might indicate problematic cases. These possibly require longer ongoing (specialist) treatment.

Baseline “psychotherapy/specialist-interview” was significantly associated with increased longterm-DTPQ-nonrecurrence. “Antidepressants” was significantly associated with decreased longterm-DTPQ-nonrecurrence. Neither was significantly associated with longterm-DTPQ-persistence of ongoing treatment.

Subgroup-proportions of *longterm-DTPQ-nonrecurrence* within 3 years compared to longterm meta-analyses: Among 4,660 patients with “antidepressants,” 23.6% had *longterm-DTPQ-nonrecurrence* (Table 2d). Among 119 patients with antidepressants, 40% had no recurrence within 1–2 years (Gloaguen, Cottraux, Cucherat, & Blackburn, 1998). Among 2,579 patients with “psychotherapy/specialist-interview,” 47.8% had *longterm-DTPQ-nonrecurrence* (Table 2d). Among 1,880 patients receiving cognitive psychotherapy, 46% had no recurrence within 2 years (12/28 studies used major-depressive-episode-criteria; Vittengl, Clark, Dunn, & Jarrett, 2007). Numbers compared despite “low-threshold” inclusion of medical specialist interviews (Section 2.4).

RCT-results on longterm-effects of antidepressants on recurrence were not contradictory (Hughes & Cohen, 2009). A naturalistic, unadjusted longterm-study confirmed our results: “Patients with a recurrent type of illness were *more often* treated with antidepressants [...] during their first episode than patients with only one episode of depression” (van Weel-Baumgarten, van den Bosch, Hekster, van den Hoogen, & Zitman, 2000, p. 61).

Baseline “antidepressants” treatment was not significantly associated with *longterm-DTPQ-persistence*. Contradictory, Gilchrist and Gunn (2007) identified antidepressant use as a *risk factor* for persistence in 17 observational studies. However, 10/6/1 studies followed up below/exactly/beyond 12 months and frequently undercut a reasonable minimum cut-off-definition for “persistence” (Section 4.1, Table 2a, Supporting Information).

RCT-results on longterm effects of psychotherapy on recurrence were confirmatory (Steinert, Hofmann, Kruse, & Leichsenring, 2014b). However, we did not strictly measure “psychotherapy,” but included interviews ≥ 10 min by neurologist/psychiatrist/medical-specialists. Patients with new-onset diagnosed depression receiving “psychotherapy/specialist-interview” early on had a significantly increased likelihood of longterm-DTPQ-nonrecurrence.

We found seemingly good comparability to RCT-results. However, we analysed “effectiveness” of crudely categorised ordinary clinical

practice (hierarchy) without randomisation and only partial adjustment for confounding factors (Section 4.4.3). In real-world care, length of antidepressants use (Ufer et al., 2007) and dosage (Riedel-Heller, Matschinger, Schork, & Angermeyer, 2001; van Weel-Baumgarten, van den Bosch, et al., 2000) might sometimes undercut guideline recommendations. We assume possible short-time/low-dosage antidepressants use *moderate* the reported effect of “antidepressants treatment” (Melfi et al., 1998).

Psychotherapy/medical specialist interventions are fully covered by SHI but not prescribed as easily as antidepressants. Patients need to enforce it and choose a therapist (IQWiG, 2016). Characteristics (preferences) of patients (providers) selecting (assigning) psychotherapy early on appear to moderate longterm-DTPQ-nonrecurrence (Ioannidis, 2016; Schomerus et al., 2013).

Intense baseline treatment in “hospital” or with “psychotherapist/specialist-interview and antidepressants” possibly covers more “problematic cases” with, for example, difficult diagnostic clarification, therapy resistance, or acute endangerment of self/others (AWMF, 2015). Confounding by “problematic cases” needs to be considered when interpreting baseline treatment (Table 2, Table 3).

4.4 | Strengths, limitations, and generalisability

We consider the following as main strengths of our study:

- longterm, external, gapless measurement;
- a population-based sample including elderly patients;
- a sample size allowing for statistical inference especially on baseline treatment;
- restriction of data misclassification using data classification across providers and extensive exclusion of diagnosed psychiatric comorbidity (Schneeweiss et al., 2007).

4.4.1 | Missing data

Psychiatric-outpatient-clinic data were not available. Psychiatric-outpatient-clinics care for a fraction of severely ill and mentally multimorbid patients (Spengler, 2003), which we mostly excluded. Assuming negligible outcome underestimation occurred only when no same-quarter physician/hospital visit existed.

4.4.2 | Misclassification

Cross-provider-combinations mostly prohibited false-positive DTPQ (Figure 2d). The least specific and most frequent DTPQ-class was “other depression-related services PQ” (Figure 2d16). From this, we excluded single-physician-diagnoses without service codes (Figure 2d18). Still, false-positive DTPQ is detected when a confirmed depression diagnosis is wrongly retained/denoted and all selected service codes relate to coexisting physical illness. Comparably low outcomes for “other services” (Table 2) suggest that possible overestimation might be tolerable. The same holds for depression treatment with “other services” and “antidepressants” (Figure 2d15, Table 2), which might partly reflect maintenance/prophylaxis treatment.

Among antidepressant users, 8.7% ($n = 601$) had their first prescription before their first diagnosis (Section 2.5). DTPQ-measurement began before diagnosed observations. Detection “inequality” caused relative overestimation of *time-to-first-DTPQ-discontinuation*. *Longterm-DTPQ-persistence* or *longterm-DTPQ-nonrecurrence* was assumingly not relevantly affected. Despite a subsequent diagnosis (Section 2.4), few of these patients still possibly used antidepressants for another indication (Melfi & Croghan, 1999). Their DTPQ-onset was misclassified too early. They were possibly misclassified for “antidepressants.” We assume this bias to be negligible among $n = 6,948$ classified antidepressant users.

4.4.3 | Residual confounding

Multivariate analysis lacked controls for “education” (Wittchen & Uhmann, 2010), “physical illness” (Beekman et al., 2001), “social support” (Leskela et al., 2004), “low mastery” (Wittchen & Uhmann, 2010), and “problematic cases” (AWMF, 2015). Physicians seemingly frequently diagnose “F32.x,” whereas patient history suggests “F33.x” (Wiegand et al., 2016). Thus, we incompletely approximated relevant “previous episodes (F33.x)” (Steinert et al., 2014a). Missing or incomplete variables suggest overt bias in our estimation of explanatory variables.

4.4.4 | Generalisability

Sample selectivity and design suggest overestimation of *longterm-DTPQ-persistence*, *longterm-DTPQ-recurrence*, *time-to-first-DTPQ-discontinuation*, and *total-time-spent-with-DTPQ*.

The case definition-criterion “two outpatient diagnoses within two different quarters in 2007” (Section 2.3, Figure 1b) excluded “low-threshold” patients with one-off diagnoses, inherently prolonged initial outcome measurement, and underrepresented primary care patients (Section 2.8).

We excluded 14% of patients dying, switching sickness fund, and going abroad (Figure 1e). Excluding suicides or presumably more healthy/active patients generates persistence/recurrence overestimation.

Results comparison might suggest “overall comorbidity neutrality” (Section 4.1). However, we do not know whether our results hold for a majority of patients with existing/upcoming psychiatric comorbidity.

4.5 | Conclusion

Fourteen percent of patients never discontinued a defined minimum depression treatment for 16 + 1 quarters. Thirty-four percent never resumed depression treatment within 3 years. Depression treatment covered ~54% of person-time within 4 years. Patients took three quarters or ~9 months median time-to-first-discontinuation. This compared to landmark survey outcomes for “total symptoms absence” or “presence of at least residual symptoms,” despite sampling differences.

The German Social Code Book IX for rehabilitation services defines *disability* as “six and more months of deviating health status. Many patients might be eligible for rehabilitation services but possibly not use/receive them (SVR, 2001). Six to 8 weeks of follow-up in most antidepressant-RCTs might not suffice for sustainable outcomes measurement for acute/maintenance/prophylaxis therapy.

Multivariate analysis generated hypotheses about causation: Women had more “episodic depression treatment” (*longterm-DTPQ-recurrence*, *total-time-spent-with-DTPQ*) than men, possibly influenced by generally more frequent utilisation. Women differed not in “chronic depression treatment” (*time-to-first-DTPQ-discontinuation*, *longterm-DTPQ-persistence*). Being retired was equally associated with increased persistence and nonrecurrence. We suggest research/interventions for retirement transition and more detailed research on frequent early retirement.

Starting treatment intensely in “hospital” or with “psychotherapy/specialist-interview and antidepressants” meant 1.8-fold likelihood of *longterm-DTPQ-persistence* but did not relevantly influence *future longterm-DTPQ-nonrecurrence*. We suggest secondary prevention interventions for incident intense users.

New-onset treatment with “antidepressants” (“psychotherapy/specialist-interview”) meant 0.54-fold (1.40-fold) likelihood of *longterm-nonrecurrence* of depression treatment. Possible short-time/low-dosage antidepressants use and patient self-selectivity for psychotherapy/specialist-interview might moderate this partly adjusted longterm finding in real-world care.

We suggest further testing of longitudinal cross-provider-data-linkage to measure “treatment-free-time,” especially stratified by comorbidity, to quantify this study’s possible selectivity and possible misclassification by comorbidity.

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