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Going beyond cost-effectiveness: analyzing routine mental healthcare data and stakeholders' perspectives to improve depression care

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CHAPTER 3

Real-world treatment costs and care utilization in patients with major depressive disorder with and without psychiatric comorbidities in specialist mental healthcare

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ABSTRACT

Background: The majority of patients with major depressive disorder (MDD) have comorbid mental conditions.

Objectives: Since most cost-of-illness studies correct for comorbidity, this study focuses on mental healthcare utilization and treatment costs in patients with MDD including psychiatric comorbidities in specialist mental healthcare, particular patients with a comorbid personality disorder (PD).

Methods: The Psychiatric Case Register North Netherlands contains administrative data of specialist mental healthcare providers. Treatment episodes were identified from uninterrupted healthcare use. Costs were calculated by multiplying care utilization with unit prices (price level year: 2018). Using generalized linear models, cost-drivers were investigated for the entire cohort.

Results: A total of 34,713 patients had MDD as primary diagnosis over the period 2000-2012. The number of patients with psychiatric comorbidities was 24,888 (71.7%), including 13,798 with PD. Costs were highly skewed, with an average cost per treatment episode of €21,186 (SD: €74,192, median: €2,320). Major cost drivers were inpatient days and daycare days (50% and 28% of total costs), occurring in 12.7% and 12.5% of episodes, respectively. Compared with patients with MDD only (€11,612), costs of patients with additional PD and with or without other comorbidities were respectively, 2.71 ($p < .001$) and 2.06 ($p < .001$) times higher and were 1.36 ($p < .001$) times higher in patients with MDD and comorbidities other than PD. Other cost drivers were age, calendar year, and first episodes.

Conclusions: Psychiatric comorbidities (especially PD), in addition to age and first episodes drive costs in patients with MDD. Knowledge of cost drivers may help in the development of future stratified disease management programs.

INTRODUCTION

Major Depressive Disorder (MDD) is a highly prevalent mental disorder, with more than 264 million people affected worldwide in 2017¹. In the Netherlands, the lifetime prevalence of MDD is estimated at around 18.7% with a 12-month prevalence of 5.2%². This is comparable to the prevalence in other high-income countries (14.6% and 5.5% respectively)³. MDD has major impact on patients' lives and is associated with limitations in multiple dimensions of functioning, both physical and social. Those limitations are comparable to or worse than those of patients with other chronic medical conditions such as arthritis and diabetes⁴. In addition, it involves considerable loss in productivity and work cut-back⁵. Hence, MDD is a large burden for society, remaining one of the leading causes of years lived with disability¹ and total disability-adjusted life-years globally^{6,7}. It is expected to be among the top three diseases with the highest global burden of disease in 2030⁸.

MDD often has a chronic-intermittent course⁹. In specialist mental healthcare settings, where patients are more severely depressed, recurrence rates are high; after five years, 60% of patients have experienced a recurrent depression, and this rate increases to 85% after fifteen years¹⁰. Around 57% of patients diagnosed with depression or anxiety who recently visited their GP received professional treatment in the general practice setting or the mental healthcare setting¹¹. Currently, depression is one of the most expensive diseases in the Netherlands, with an expenditure of almost 1.1 billion Euros annually (at least 1.3% of the total expenditure on health and welfare)¹².

Previous research has shown that patients with MDD often have other mental disorders^{13,14}. The course of illness for patients with MDD and coexisting mental or physical illnesses is less favorable. They have more severe symptoms, lower levels of functioning, and less recovery than patients with MDD alone¹⁵. The prevalence of a comorbid personality disorder (PD) in patients with MDD is high at 45% and rises to 60% in patients with dysthymic disorders¹⁶. Although the majority of studies demonstrated that a comorbid PD with MDD was associated with poorer outcomes for depression than MDD alone¹⁷⁻¹⁹, other studies found no differences (at long-term follow-up)^{19,20} or did find a negative effect on depression outcome but not on functioning or quality of life outcomes²¹. Looking at healthcare utilization, patients with PD had more psychiatric inpatient, outpatient, and pharmacological treatment than patients with MDD as a single diagnosis²². Additionally, patients with MDD and comorbid PD were more likely to have hospitalizations, higher rates of recurrent depressions, longer mean length of stay²³, and a longer duration of depressive episodes than patients with without comorbid PD²⁴.

Several studies have investigated the direct and indirect costs of MDD from a societal perspective²⁵⁻³⁰. The healthcare costs associated with MDD in primary care patients have also been a focus of research^{31,32}. Several cost-of-illness studies evaluated MDD with comorbid somatic disorders^{33,34} or allowed for MDD-related treatment/costs³⁵. At

the same time, these studies included relatively short follow-up times of 1-2 years. One study demonstrated that the overall effect of neuroticism, a personality characteristic, on the use of somatic and mental healthcare was associated with enormous economic costs, exceeding those of common mental disorder, including mood disorders³⁶. To our knowledge, no studies have investigated in detail the treatment costs of patients with MDD and other psychiatric comorbidities in the specialist mental healthcare setting in unselected observational data with a large follow-up time. The impact of various psychiatric comorbidities, including PD, on healthcare utilization and treatment costs remain underexposed.

The aims of our study were to (1) compare specialist mental healthcare utilization and related costs of treatment episodes in patients diagnosed with MDD with and without psychiatric comorbidities, with a particular focus on a comorbid PD, and (2) investigate which patient characteristics and clinical variables were driving treatment costs.

METHODS

Data Source

For this retrospective observational study, we used a large administrative mental healthcare database: Psychiatric Case Register North Netherlands (PCRNN). This register contained patient-level specialist mental health service use and clinical diagnosis data for patients in the northern region of the Netherlands (1.7 million inhabitants) between 1 January 2000 and 31 December 2012. In the PCRNN, data were available for the majority of specialist mental healthcare organizations (approximately 75%) providing care to patients with moderate to severe mental health disorders. The PCRNN data consisted of patient demographics, main and secondary diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) ³⁷, and the date and type of mental health service use. Usage of mental health services was divided into five categories: (1) inpatient day (24-h treatment), (2) day treatment, (3) psychiatric home care service, (4) community-based daycare and (5) outpatient visit.

Study Population

We included patients registered with unipolar MDD as primary diagnosis and who had at least one record of mental health service use in the PCRNN. We included the following DSM-IV diagnosis codes: 296.2-296.36³⁷. We distinguished between patients with and without a comorbid PD (DSM-IV codes: 301.0-301.9) diagnosed in the cohort period of the study. We also distinguished between the presence or absence of other psychiatric comorbidities, including anxiety disorders, bipolar disorders, schizophrenia disorders, substance use disorders, and a category 'other' covering the remainder of disorders. For more information regarding the definitions of the psychiatric comorbidities, see

Supplementary Material A. We distinguished four groups of patients: (1) patients with MDD only, (2) patients with MDD and other psychiatric comorbidities other than PD, (3) patients with MDD and comorbid PD without other psychiatric comorbidities, and (4) patients with MDD and other psychiatric comorbidities, including PD.

Defining treatment episodes

Mental healthcare costs were estimated per treatment episode. The first treatment episode started with the first mental health service use record after the date of MDD diagnosis as primary diagnosis. The end of a treatment episode was the last mental health service use record after which no mental health service contacts were registered for six consecutive months. The first mental health service use contact after six consecutive months with no mental health service use contacts marked the start of a subsequent treatment episode. From January 1st, 2013 the PCRNN database ceased to exist in that form, therefore no data was available after December 31st, 2012. Treatment episodes that started after July 1st 2012, were considered censored episodes. These episodes were excluded from the analysis as they may have resulted in higher costs if they continued in 2013. The end date of each patient's last follow-up was determined when no mental health service contacts were registered for six consecutive months within the cohort period.

A first treatment episode could be distinguished into an episode without any mental health service use in the cohort period prior to MDD diagnosis and, an episode with previous mental health service use for treatment not related to MDD in the cohort period.

Outcome Measures

Outcomes of interest were average and median costs of treatment episodes in patients with MDD as primary diagnosis with and without other psychiatric comorbidities. Subsequently, drivers of treatment costs (patient characteristics [sex, age] and clinical variables [presence of psychiatric comorbidities, including PD, and first or subsequent treatment episode] were investigated. Sex, age, MDD diagnosis, and first or subsequent episode were measured prior to the treatment episode. The presence of psychiatric comorbidities was measured either at baseline or during an episode. Frequency counts and percentages were used to summarize categorical variables. We reported both means and medians for continuous variables because costs and episode duration were highly skewed. Differences in costs between these four groups of patients were compared.

Data Analytic Procedures

Patient characteristics, mental health service use, treatment episode duration, and treatment costs per treatment episode were summarized descriptively. Treatment

costs in specialist mental healthcare did not include treatment costs related to other non-mental-health related chronic conditions. In this study, we used the healthcare perspective, applying unit prices of the five health service use categories to calculate the direct costs of treatment³⁸. The five types of health service use were valued using unit costs per category and summed per treatment episode. Unit prices were taken from the Dutch Costing Manual of the National Health Care Institute³⁸ and indexed at the price level of year 2018. Comparisons of group characteristics were analyzed using either analysis of variance or generalized linear model (GLM) for continuous outcomes, Kruskal-Wallis test or Mann-Whitney test for non-normally distributed continuous or ordinal outcomes for two or more groups, or chi-squared (χ^2) test for categorical outcomes. Within the group comparisons, a Bonferroni correction was applied to correct for multiple testing.

A GLM with a gamma distribution and a log-link function was used to assess cost drivers of treatment in the PCRNN cohort. In the analyses, we additionally corrected for treatment episode duration, as cost of treatment will depend on duration (together with intensity) of treatment. The GLM permits flexible modelling of covariates and is recommended for right-skewed, non-normally distributed data, which usually applies to cost data³⁹. Models were compared by using the Akaike information criterion (AIC), and the best fitting model is presented.

Depending on the type of test, a *p*-value of < 0.05 or the Bonferroni-corrected *p*-value determined statistical significance. All analyses were conducted using STATA/SE version 16.0 (StataCorp LLC, College Station, Texas, USA).

Sensitivity analyses

Sensitivity analyses were performed on the definition of treatment episodes by varying the time gap allowed between mental health service contact moments. In the sensitivity analyses, the start of a treatment episode was defined similarly, i.e., as the first mental health service contact after the date of MDD as a primary diagnosis. We defined the treatment episode as having ended when no mental health service use contacts were registered for three and nine consecutive months, respectively. After this period, the first consecutive mental health service use record was considered the start of a subsequent episode, and so on.

RESULTS

Study Population

The demographic and clinical characteristics of the study sample are shown in Table 1. Of the 34,713 patients, 61.8% were female, and the average age was 44.3 years (SD: 18.3) at first MDD diagnosis in the specified cohort period. Almost two-thirds of the patients

diagnosed with MDD had one treatment episode in specialist mental healthcare, and over one-third of the patients had one or more subsequent treatment episodes during the cohort period. After the removal of nine patients with missing sex data and 2,420 censored episodes, 52,667 treatment episodes remained. There were no missing values for the other variables in our data. Over 70% of the patients had psychiatric comorbidities and 39.7% of the patients of the entire cohort were diagnosed with a comorbid PD.

Costs of first versus subsequent treatment episodes

Table 2 shows the costs for first and subsequent treatment episodes for the entire group of patients diagnosed with MDD with or without any comorbidities. The average cost of a treatment episode was € 21,186 (SD: €74,192), with a median cost of €2,320 (not shown in table).

Table 1. Demographic and clinical characteristics of the study sample

Variable	N=34,713
Sex, % female	61.8%
Age at the time of first MDD diagnosis, % of total sample	
<18	5.1%
18-65	80.5%
>65	14.4%
Mean years (sd)	44.3 (18.3)
Number of treatment episodes after MDD diagnosis, % of total sample	
1	65.0%
≥2	35.0%
Range	[1-10]
Comorbid Personality Disorder, % yes	39.7%
Number of psychiatric comorbidities (including Personality Disorder)	
MDD only	9,825
1 additional diagnosis	12,504
2 additional diagnoses	8,292
3 additional diagnoses	3,479
4 additional diagnoses	552
5 additional diagnoses	57
6 additional diagnoses	4
Follow-up time in the cohort, days	
Mean (sd)	1,209 (1,173)
Median	773

MDD: major depressive disorder

Comparing the differences in mean costs between the three types of episodes using a Kruskal-Wallis H test, as well as a GLM with gamma distribution and log-link function, showed that the mean costs of the three types of treatment episodes differed significantly. First episodes of patients with a history of mental health service use for a non-MDD-related psychiatric diagnosis were 0.74 times cheaper ($p < .001$, 95% confidence interval [CI]: 0.68-0.81) than the first episodes of patients without a history of mental health service use for a non-MDD-related psychiatric diagnosis. Mean costs

of subsequent episodes were 0.43 times cheaper ($p < .001$, 95% CI: 0.40-0.46) than the first episodes of patients without a history of mental health service use for a non-MDD-related psychiatric diagnosis.

The average duration of treatment for the entire study sample was 579 days (± 19 months), with a median duration of 308 days (± 10 months). In 25% of the cases, the treatment episodes lasted longer than 700 days. The duration of a treatment episode differed significantly between the three types of episodes ($F(2, 52,664) = 989.24$, $p < .001$ and $\chi^2(2) = 2,894$, $p < .001$) with the longest duration for a first treatment episode in patients with no history of mental health service use and shortest in a subsequent episode.

Table 2. Costs of treatment episodes

	First treatment episodes		Subsequent treatment episodes	p-value
	No history of mental health service use	History of mental health service use		
N	25,976	8,737	17,954	
Treatment costs per episode, 1,000 €				
Mean (sd)	27.8 (91.0)	20.7 (65.7)	11.9 (43.7)	< .001*
Median	3.1	2.6	1.3	
Treatment duration, days				
Mean (sd)	704 (905)	626 (758)	376 (509)	< .001*
Median	372	350	202	

* Significant p-value for all subgroups

Patient characteristics, mental health service use and treatment costs of MDD patients with and without psychiatric comorbidities

Table 3 presents the patient characteristics, mental health service use, and treatment costs of the four defined patient groups defined in Section *Study Population*. Major cost drivers for the entire cohort were inpatient days and day care days (50% and 28% of total costs). These occurred in 12.7% and 12.5% of episodes, respectively (not shown in Table 3). Patients' sex differed significantly in the groups 1 and 2 ($\chi^2(1) = 24.86$, $p < .001$), groups 2 and 4 ($\chi^2(1) = 13.53$, $p < .001$) and groups 2 and 3 ($\chi^2(1) = 17.49$, $p < .001$). A statistically significant difference between the underlying distributions of age was found in all groups of patients ($F(3, 34,709) = 441.58$, $p < .001$).

The number of subsequent treatment episodes differed significantly between the four groups ($\chi^2(3) = 3700$, $p < .001$). Subsequent treatment episodes occurred the least in group 1 and were most frequent in group 4. Furthermore, the four groups differed significantly from each other in the amount of mental health service contacts per treatment episode ($\chi^2(3) = 1839$, $p < .001$), treatment episode costs ($\chi^2(3) = 1778$, $p = .0001$), and treatment durations ($\chi^2(3) = 1617$, $p < .001$). Treatment episode duration was the

Table 3. Patient characteristics, mental health care contacts and treatment cost in patients with Major Depressive Disorder with and without psychiatric comorbidities

	Patients with MDD only (1)	Patients with MDD and other CM, without PD (2)	Patients with MDD and PD, without other CM (3)	Patients with MDD, PD, and other CM (4)	p-value
Number of unique patients	9,825	11,090	3,659	10,139	
Number of episodes	11,885	17,235	4,812	18,735	
Sex, % female	63.1%	59.7%	62.6%	63.6%	< .001*
Age, years					
Mean (sd)	49.1 (19.2)	42.1 (19.1)	47.1 (16.3)	41.0 (15.7)	< .001*
Subsequent treatment episodes, %	15.0	39.0	23.1	54.	< .001*
Mental health service use per treatment episode, absolute numbers					
Total, Mean (sd)	63 (202)	83 (257)	133 (342)	164 (391)	< .001*
Total, Median	13	17	24	28	
Inpatient days					
Mean (sd)	150 (377)	190 (461)	202 (480)	233 (483)	
Median	69	76	79	84	
In total episodes, %	12.3	14.5	16.7	22.0	
Day treatment days					
Mean (sd)	170 (253)	165 (248)	242 (349)	222 (322)	
Median	102	91	137	119	
In total episodes, %	9.9	12.2	17.9	23.1	
Psychiatric home care service visits					
Mean (sd)	20 (40)	20 (40)	41 (84)	40 (88)	
Median	10	10	13	12	
In total episodes, %	5.8	7.6	10.2	12.4	
Community-based day care center visits					
Mean (sd)	195 (290)	192 (315)	219 (306)	162 (265)	
Median	59	56	88	58	
In total episodes, %	1.8	2.6	4.6	5.7	
Outpatient visits					
Mean (sd)	23 (41)	29 (46)	41 (63)	47 (82)	
Median	11	14	18	19	
In total episodes, %	99.3	99.4	99.5	99.5	
Total cost per treatment episode, €					
Mean (sd)	11,612 (49,534)	15,798 (64,586)	23,933 (77,271)	31,509 (91,340)	< .001*
Median	1,508	1,972	2,900	3,480	
Duration treatment episode, days					
Mean (sd)	439 (631)	492 (647)	733 (946)	709 (895)	< .001*
Median	233	284	370.5	384	

MDD: major depressive disorder
 CM: comorbidities (psychiatric)
 PD: personality disorder
 * Significant p-value

shortest in group 1 and 2 and longest in group 3 and 4. Median costs of treatment episodes increased from €1,508 in patient group 1 to €3,480 in group 4. Patients with a comorbid PD (group 3 and 4) more often had different types of mental health services than patients with MDD without PD (group 1 and 2).

Relation between patient and clinical characteristics and treatment costs

Table 4 presents the results of the GLM with a log-link and gamma-distribution. The GLM model was selected based on the best AIC and Log likelihood statistic (see Supplementary Material B). Higher age, the presence of psychiatric comorbidities, year of start treatment episode, and a first treatment episode after MDD diagnosis were significantly associated with higher treatment costs. A subsequent treatment episode was negatively associated with treatment costs.

Table 4. Relation between patient and clinical characteristics and mental healthcare use costs

Characteristic	Coefficient Exp(b)	Standard Error	95% CI	p-value
Patient group (ref = MDD only)				
MDD, CM, no PD	1.2319	0.0325	1.1699; 1.2972	< 0.001*
MDD, PD, no CM	1.2745	0.0460	1.1875; 1.3680	< 0.001*
MDD, PD, CM	1.7799	0.0491	1.6861; 1.8789	< 0.001*
Female sex (ref = male)	1.0279	0.0193	0.9907; 1.0665	0.144
Age (years)	1.0055	0.0005	1.0045; 1.0065	< 0.001*
Year of start treatment episode (ref = 2000)	1.0072	0.0028	1.0016; 1.0128	0.011*
Treatment episode recurrence (ref = first)				
Subsequent	0.7667	0.0156	0.7367; 0.7979	< 0.001*
Treatment episode duration (days)	1.0018	0.00002	1.0017; 1.0018	< 0.001*
Constant	2020	90	1,852; 2,203	< 0.001*

MDD: major depressive disorder

CM: comorbidities (psychiatric)

PD: personality disorder

*: Significant p-values

Sensitivity Analyses: Varying the definition of treatment episodes

Table 5 presents the results of the sensitivity analyses. Using a treatment episode definition of three consecutive months of no mental health service use, the median duration of a treatment episode (167 days) was lower than the definition of six months (308 days) or nine months (371 days). In the sensitivity analysis using a treatment episode definition of nine consecutive months of no mental health service use, mean and median costs of a treatment episode approached the six-month definition (mean: ±€ 22,500, median: ±€2,550).

The variables that were consistently (significant or insignificant in all sensitivity analyses) associated with treatment costs were age, patient group (group 1-4), year of treatment episode start, and whether the treatment episode was a first or subsequent episode. In the sensitivity analyses, sex was not consistently associated with treatment costs.

Table 5. Sensitivity analyses

	3 months	6 months	9 months
Duration treatment episode, days			
Mean (sd)	358 (572)	579 (780)	683 (864)
Median	167	308	371
Patients with subsequent treatment episodes, %	51.2	35.0	28.4
Costs of treatment episode, €			
Mean (sd)	14,916 (61,978)	21,186 (74,192)	23,655 (78,467)
Median	1,160	2,320	2,784
Gap between treatment episodes, days			
Mean (sd)	363 (457)	641 (554)	812 (575)
Median	171	418	610

DISCUSSION

This observational cohort study showed that the treatment of patients with MDD and psychiatric comorbidities in specialist mental healthcare involved more health service use and higher costs than treatment of patients with MDD only. In particular, a comorbid PD resulted in more health service use and costs compared to other psychiatric comorbidities. These findings underscore the importance of disease management programs targeting patients with a combination of disorders. For the entire group of patients, a first treatment episode was significantly and robustly more costly than a subsequent treatment episode. Higher age, coexisting psychiatric disorders including PD, and year of treatment start were significantly associated with higher treatment costs.

We observed a median treatment duration of ten months, and almost one-quarter (23%) of the study population remained in treatment after two years. Previous epidemiological studies had found depressive episode durations of 3-12 months^{40,41}. Spijker et al. found that approximately 20% of patients sampled from the general population had not recovered in 24 months⁴¹. Our results seem comparable.

In our study sample, only three out of ten patients were diagnosed with MDD only. Investigating the costs for the different groups provided a more complete view on actual mental health services utilized and costs per patient. The population of our study sample demonstrated that the majority of patients with MDD have other psychiatric comorbidities that are associated with additional mental health service use and costs.

Cost-of-illness studies that focus on the isolated costs of MDD only provide an overview of costs for a minority of patients with MDD in the real world.

At the time of MDD diagnosis, the mean age of patients in our study population was 44 years. Their age was not related to the age of first depressive episode but was related to the age of first treatment episode after MDD diagnosis in specialist mental healthcare. Patients are often treated by the GP or in primary mental healthcare before referral to specialist mental healthcare. Patients with comorbidities were younger on average. This might be because of an increased tendency to seek help more quickly in people with MDD and psychiatric comorbidities than in people with MDD only⁴².

Compared to the rates of recurrence of depression episodes found in the literature¹⁰, the proportion of subsequent treatment episodes in our study was relatively low (35.0%). It is possible that a proportion of these patients had subsequent treatment outside the specialist mental healthcare setting. In addition, we only had a maximum of 12 years of follow-up time, with an average follow-up time of 1209 days.

GLM analysis showed that a subsequent treatment episode was associated with lower treatment costs. In a previous study, a recurrent depressive episode also predicted shorter durations of depressive episodes⁴¹. Presumably, patients with a recurrent depression better recognize the signals of the disorder and seek treatment more quickly. They might have also learned how to better cope with a depressive episode because of prior experiences. Furthermore, age and hospitalizations were significant cost drivers in other cost-of-illness studies^{26,29,43}, with hospitalizations being a major cost component. In our study, hospitalizations were also a major cost driver, contributing to 50% of total costs, though only occurring in 12.7% of the episodes.

The sensitivity analyses demonstrated that, in the episode definition of three months, almost 20% of the treatment episodes lasted less than two weeks. This could indicate that a three-month gap is likely too short and not suitable in the definition of treatment episodes. In the nine-month definition, median duration and median costs of treatment episodes were more comparable to those of the six-month definition, indicating that these definitions approached the actual treatment episode.

Our study sample was selected based on a primary MDD diagnosis. The additional costs in patients with comorbidities likely reflect longer treatment due to disease complexity or the use of combination treatment. Combination treatment is not always obvious, for instance when elements of cognitive behavioral treatment for depression can also affect personality aspects. Our findings showed that the combination of MDD and comorbid PD resulted in more mental health service use and costs than MDD and other psychiatric comorbidities. However, we cannot draw any conclusion with regard to the exact costs that were attributable to combination or more intensive treatment in case of comorbidities. Given the excess costs and care utilization, disease management programs should target both PD and MDD, maybe more than is currently done, for example, integrated treatment or combined treatment instead of several disorder-

specific or consecutive treatments⁴⁴. Conceptualising and treating MDD as an isolated disorder may underestimate the prognosis of the majority of patients and the type of care that is appropriate⁴⁵.

Several strengths and limitations of this study should be taken into consideration. A major strength is that mental health service utilization and related costs were tracked over a long period of time. Data in the PCRNN contained actual utilized mental health services and clinical diagnoses, which are not based on self-report questionnaires. The latter are often prone to recall bias. Furthermore, in a relatively large sample, isolated episodes of care could be identified. This made it possible to compare the costs of treatment episodes of patients with MDD only and those with additional psychiatric comorbidities during the available timeframe. Although our study focused on PD, it would be interesting to compare other psychiatric comorbidities in future studies, given the available sample size.

A first limitation of the study is that information regarding the costs of medication usage was unavailable. However, we expect that medication use is relatively stable over the duration of an episode and would only be a minor part of the costs. The most prevalent antidepressants (fluoxetine, paroxetine, fluvoxamine, citalopram, sertraline and paroxetine) cost less than 1.20 Euros per day⁴⁶.

A second limitation was that the number of variables concerning patient characteristics (e.g., occupation, education) were unavailable. This is one disadvantage of using a large real-world observational dataset as opposed to a designed but smaller study cohort. In addition, it might be possible that a comorbidity is identified during a treatment episode. We expect that the impact of this limitation is small, as symptoms are likely present at the start of the episode than to manifest during treatment.

A third limitation is that the data used in our study are somewhat outdated. The epidemiology of MDD remained relatively stable over time, and the available evidence-based treatments are mostly still valid in current treatment guidelines. Therefore, we believe that a better understanding of the mental health service utilization and costs of treatment and the role of psychiatric comorbidities on these remain relevant at this time.

Another limitation of our study is that we could not ascertain new-onset MDD diagnosis. MDD diagnoses prior to an individual's inclusion in the cohort were not available and might have been present, especially among individuals who were older in their cohort's first episode. This could impact our findings, as the number of past diagnoses might significantly affect treatment costs and service use. However, the 12-year follow-up time of our dataset partially addresses the problem of not being able to ascertain new-onset episodes. In addition, we distinguished between first treatment episodes for patients diagnosed with MDD with or without a history of specialist mental health service use for a non-MDD-related psychiatric diagnosis and subsequent treatment episodes in our cohort.

Finally, no information regarding reasons for treatment termination was available, so we do not know whether treatment episodes were terminated because of recovery or for other reasons. Patients in specialist mental healthcare might also be referred back to generalist mental health services when only residual symptoms are present. In such cases, a treatment episode does not end but continues in a less intensive mode. We performed sensitivity analyses to account for this lack of information.

CONCLUSION

The majority of patients with MDD in specialist mental healthcare have psychiatric comorbidities. Cost-of-illness studies that focus on MDD alone underestimate mental healthcare costs for most patients with MDD. This is especially true for a comorbid PD, which makes treatment longer and more costly. A better understanding of the costs of treatment episodes in specialist mental healthcare may help identify patients at risk of burdensome treatment trajectories, thereby providing the opportunity for future stratified disease management programs.

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Supplementary Material A. List of DSM-IV codes used to define psychiatric comorbidities

Category	DSM-codes
Depressive disorder	296.2x and 296.3x
Personality disorder	301.x
Anxiety disorders (25.3%)	300.x
Bipolar disorders (3.5%)	296.0x 296.4x 296.5x 296.6x 296.7 296.8x
Schizophrenia disorders (3.5%)	295.x 297.1 298.8 298.9
Substance use disorders (8.9%)	291.x 292.x 303.x 304.x 305.x
'Other' (53.9%)	The codes not mentioned above. In the data this meant the following codes: 100 200 290.x 293.x 294.x 295 296.1 296.9x 297.3 297.9 299.0 299.8 302.x 306.x-319.x 400 500 600 700 900-906 V61.x V62.x V65.0

Supplementary Material B. Goodness of fit statistics of the different GLM models

GLM Model (with gamma distribution and log link function)	AIC statistic	Log Likelihood statistic	BIC statistic
Gender only	21.912	-577,022	-365,353
Age only	21.897	-576,626	-366,145
Treatment episode duration only	20.220	-532,460	-454,476
Patient group only	21.764	-573,106	-373,163
Year of start treatment episode only	21.467	-565,301	-388,794
Treatment episode recurrence only	21.747	-572,667	-374,063
Complete model with all variables above	20.170	-531,136	-457,049
Complete model without gender	20.170	-531,140	-457,050
Complete model without treatment episode duration	21.167	-557,384	-404,563

