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Seasonality of antidepressant prescriptions and sick leaves

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ABSTRACT

The aim of the present study was to estimate the number of patients with a seasonal prescription pattern of antidepressants, which might be taken as a surrogate marker for medicated patients with seasonal affective disorder (SAD). Furthermore, we examined the time course of sick leaves for patients with seasonal and non-seasonal prescriptions of antidepressants. A retrospective analysis of prescription data of all patients insured by the Sickness Fund Burgenland (BGKK) between 2005 and 2016 was performed. Patients with treatment initiation of an antidepressant in the last and first quarter of the year for at least two consecutive years were selected (SAD-med). Patients with continuation treatment in the third quarter and patients with initiation of antidepressant medication in the second and third quarter of the year were excluded. The mean yearly prescription rate for antidepressants was 9.6% in the insured population. 3.0% of patients treated with antidepressants and 0.9% of insured cases satisfied the definition of SAD-med. The mean number of yearly sick leave days was similar for SAD-med patients and those with non-seasonal prescriptions. Time series analysis showed that sick leaves in SAD-med were influenced by seasonal fluctuations for several years after the first antidepressant prescription. Our study sheds light on antidepressant prescription and sick leave patterns in the general population. Compared to the prevalence of SAD, the estimated rate of SAD-med is substantial. Sick leaves appear to be closely linked to antidepressant prescriptions, and show a characteristic time course before and after the initial prescription.

1. Introduction

Seasonal affective disorder (SAD) is a subtype of mood disorder characterized by recurrent depressive episodes during fall and winter with subsequent remission or hypomanic/manic episodes during the next spring/summer period (Rosenthal et al., 1984). The prevalence of SAD according to DSM-IV/5 criteria (American Psychiatric Association, 2000, 2013) in the general population has been estimated between 2.4% and 3.1% in temperate climates (Levitt and Boyle, 2002; Mersch et al., 1999; Michalak et al., 2001; Pjrek et al., 2016). Light therapy is the first choice of treatment for SAD (Pail et al., 2011). Antidepressant treatment is an alternative option for SAD and is often necessitated in patients with insufficient response to light therapy or logistical problems in adhering to this treatment (Pjrek et al., 2004). Previous studies investigated the clinical usage of light therapy in psychiatric hospitals (Fischer et al., 2012) and in office-based doctors (Winkler-Pjrek et al., 2016), but little is known about the actual use of psychopharmacologic medication in SAD in clinical practice.

The clinical diagnosis of SAD and most epidemiological and clinical studies on SAD rely on a history of seasonal mood episodes and are therefore subject to recall bias except in studies with a longitudinal design (Clery-Melin et al., 2018; Harmatz et al., 2000; Sakamoto et al., 1995; Wicki et al., 1992). The retrospective approach of the diagnosis of SAD was criticized before (Hansen et al., 2008; Traffanstedt et al., 2016; Winkler et al., 2017). Therefore, corroboration of the validity of SAD as a diagnostic entity by an alternative approach is an important line of research. In this regard, previous studies in other fields of medicine have used drug sales data for disease burden estimation: This has, for example been done for prescriptions of nitrates to infer the prevalence of angina pectoris (Cannon et al., 1988; Maitland-van der Zee et al., 2003), for oral hypoglycemic agents and diabetes mellitus type 2 (Sinnott et al., 2017), amphetamines and attention deficit hyperactivity disorder (Schubert et al., 2010), and anti-tuberculosis treatments and tuberculosis (Arinaminpathy et al., 2016).

Furthermore, there is a paucity of studies on the work-related consequences of SAD in comparison to non-seasonal depression. Sick

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leaves of SAD patients were studied before in clinical (Pjrek et al., 2008) and population-based samples (Mersch et al., 1999; Pjrek et al., 2016), but these studies also relied on self-reports. The main finding of these studies suggest higher levels of unemployment and more sick leave days in SAD patients than in subjects without the syndrome. Moreover, reduced productivity at work (presenteeism) seems to play a substantial role in SAD and probably also in subsyndromal SAD.

The aim of this study was to estimate the rate of seasonal prescriptions of antidepressants as surrogate marker for treated winter-type SAD in a large sample of the general population. Furthermore, we attempted to describe the pattern of sick leaves in patients with seasonal versus non-seasonal antidepressant prescriptions. We hypothesized a priori that sick leaves of patients with seasonal prescriptions would be accompanied with identifiable seasonality.

2. Method

This study was approved by the Ethics Committee of the Medical University of Vienna (EC No. 1018/2017). A retrospective analysis of prescription data of all patients insured by the Sickness Fund Burgenland (BGKK) between 2005 and 2016 was performed. During this time frame a mean number of 195135 persons (68.4% of the inhabitants of Burgenland, one of the nine federal states of Austria) were insured by the BGKK. Patients with treatment initiation of an antidepressant (ATC code N06A) between the beginning (1st October) and the end (31st March) of the fall/winter season for at least two consecutive years were selected. Patients who received further prescriptions during 1st July and 30th September (after treatment start in fall/winter) and patients with initiation of antidepressant medication between 1st April and 30th September were excluded. This definition of seasonal prescriptions was termed SAD-med. All other study subjects not satisfying this definition were considered as having non-seasonal prescriptions of antidepressants (non-SAD).

Our dataset consisted of a total of 58138 patients (29.8% of all insured persons), who received at least one prescription of an antidepressant during the 12 years of analysis. All dates of sick leaves between 2004 and 2016 were derived from the BGKK database for SAD-med patients and non-SAD patients. A total of 167121 sick leave periods were transformed using a special data converter programmed with C# and Microsoft Visual Studio 2017 (Microsoft Corporation, 2017) resulting in tabular daily sick leave data relative to the first antidepressant prescription for each single patient.

Statistical analyses were performed using the R Project for Statistical Computing (version 3.4.3) (R Core Team, 2018) together with the packages gmodels (Warnes et al., 2015), forecast (Hyndman, 2017), lmtest (Zeileis and Hothorn, 2002), and ggplot2 (Wickham, 2009).

After visual inspection, sick leave data of SAD-med and non-SAD patients from day −120 to day +2190 relative to the first antidepressant prescription were further aggregated to form time series by months. Friedman test was performed to test the null hypothesis of equal distribution of detrended data (after calculating first differences) with months as groups.

An autoregressive integrated moving average (ARIMA) model was fit to the time series both using the auto.arima method of R's forecast package (selection criteria being the Akaike information criterion [AIC], the Bayesian information criterion [BIC] and parsimony) and a stepwise manual selection process based on the autocorrelation (Acf) and partial autocorrelation (Pacf) functions of the time series and the residuals of the models as well as considering root mean square error (RMSE) and mean absolute scaled error (MASE). The ARIMA models are reported in the form $(p, d, q) \times (P, D, Q)_m$, where p is the order of the autoregressive model, d is the degree of differencing, and q is the order of the moving-average model. P, D, and Q refer to the respective terms of the (optional) seasonal part of the model, where m is the number of periods in each season.

Table 1
Demographic variables of patients in the sample.

	SAD-med	non-SAD	
N	1750 (3.0%)	56388 (97.0%)	
Sex			
Females	1116 (63.8%)	37487 (66.5%)	$\chi^2 = 5.583$, df = 1,
Males	634 (36.2%)	18901 (33.5%)	p = 0.018
Age (years, μ ± SD)	53.5 ± 17.8	55.4 ± 19.0	t = −4.339, df = 1874.3, p < 0.0001

The frequency of sick leaves was compared at four a priori defined 30 day time periods: half a year before the first antidepressant prescription (days −198 to −168), around the day of prescription (days −15 to 15), half a year (days 168–198) and one year (days 350–380) after the first prescription. For sick leave calculations only data of patients between 18 and 65 years were used and influences of shorter observation periods were accounted for. The level of statistical significance (two-tailed) was set to $p \leq 0.05$. The Bonferroni-Holm correction was applied to the p-values to correct for multiple testing where appropriate.

3. Results

The mean yearly prescription rate of antidepressants was 9.6% of all insured persons (mean 10-year prescription rate: 21.8%). The percentage of subjects with a total number of prescriptions are as follows: 1 prescription: 26.5%, 2: 11.8%, 3: 7.1%, 4: 5.1%, 5: 3.9%, 6: 3.3%, 7: 2.7%, 8: 2.4%, 9: 2.2% 10: 2.0%, 11: 1.8%, ≥12: 31.2%. We found 1750 patients (3.0% of treated patients and 0.90% of all insured cases) satisfying the definition of SAD-med (mean 10-year prevalence 2.5% and 0.74%, respectively). Table 1 displays demographic variables and group differences. The rates by year for patients with at least one antidepressant prescription and SAD-med patients are presented in Fig. 1. 79.0% of patients in the SAD-med group had seasonal prescriptions for 2 years, 15.7% for 3 years, 3.2% for 4 years, 0.9% for 5 years, and 1.2% for 6–12 years (Fig. 2).

The mean number of sick leave days per year was 17.5 ± 30.1 in all patients with at least one antidepressant prescription. A comparison of sick leave days in SAD-med and non-SAD (also subdivided by gender) is presented in Table 2. Percentages of patients being on sick leave in the SAD-med and non-SAD group for each day 1 year before to 5 years after the initial antidepressant prescription are presented in Fig. 3. Comparisons for sick leaves showed a significant difference between the time period −0.5 years before first prescription and the following predefined epochs (0, +0.5 and + 1 year relative to prescription) in SAD-med ($\chi^2 = 136.94$, df = 3, $p < 0.0001$) and non-SAD ($\chi^2 = 4234.5$, df = 3, $p < 0.0001$). Post-hoc tests revealed that compared to −0.5 years the SAD-med group had higher sick leaves at 0 years ($Z = -10.013$, $p < 0.0001$) and at +1 year ($Z = -3.023$, $p = 0.015$), but not at +0.5 years ($Z = -1.987$, $p = 0.188$), while the non-SAD group exhibited higher sick leaves only at 0 years ($Z = -8.211$, $p < 0.0001$) and 0.5 years ($Z = -11.515$, $p < 0.0001$) compared to −0.5 years. SAD-med patients had significantly higher sick leave levels than non-SAD patients 1 year after the initial prescription ($Z = -5.522$, $p < 0.0001$), but group differences were not significant at −0.5, 0 and 0.5 years (Fig. 4).

Friedman test for sick leave data in SAD-med patients using month as a factor was statistically significant ($\chi^2 = 24.169$, df = 11, $p = 0.012$), but not in non-SAD patients ($\chi^2 = 11.985$, df = 11, $p = 0.365$). An ARIMA $(0, 1, 0) \times (1, 0, 0)_{12}$ model was selected as the best model to describe monthly time series in SAD-med (RMSE = 0.132, MASE = 0.323). The seasonal AR term (estimate ± standard error: 0.550 ± 0.126) was statistically significant ($p < 0.0001$). A Box-Ljung test was applied to the residuals of the ARIMA model and found to be not significant ($\chi^2 = 24.926$, df = 24,

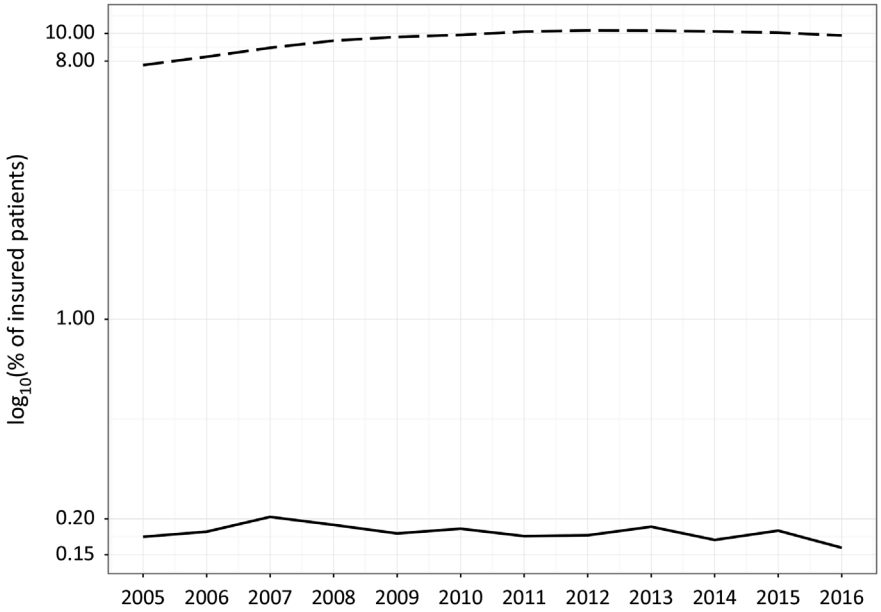

Fig. 1. Percentage of SAD-med patients (N = 1750; solid line; see method section for definition) and percentage of patients with at least one antidepressant prescription (N = 58138; dashed line) by year in all persons insured by the Sickness Fund Burgenland (BGKK) between 2005 and 2016.

p = 0.410). The best ARIMA model for non-SAD data was (1, 1, 0) without any seasonal terms (Box-Ljung test: $\chi^2 = 6.039$, df = 24, p = 0.999). Seasonal decomposition (Cleveland et al., 1990) of monthly time series data of sick leaves of SAD-med patients into seasonal fluctuations, trend and remainder is available as supplementary material.

4. Discussion

To our best knowledge this is the first study to provide comprehensive information on seasonal prescription patterns of antidepressants and associated sick leaves.

The prescription rate of antidepressants over the study period of 12 years was nearly 30% of the total population. On the other hand the adherence to antidepressants seems to be quite low: 26.5% only had a single prescription of an antidepressant with no represcriptions, which is in line with previously published data (Hinteregger et al., 2012).

Table 2
Number of sick leave days per year of SAD-med and non-SAD patients (subgroup of those between 18 and 65 years old) starting 1 year before initial antidepressant prescription to 5 years afterwards.

Sick leave days/year (μ ± SD)			
	SAD-med	non-SAD	
Total group	17.67 ± 28.09	17.45 ± 30.17	Z = −3.070, p < 0.002
Females	15.95 ± 27.31	16.05 ± 28.51	Z = −1.729, p = 0.084
Males	20.51 ± 29.14	20.07 ± 32.89	Z = −2.529, p = 0.011

These early drop-outs are problematic insofar as treatment guidelines for major depression and anxiety disorders recommend treatment periods of 6 months or longer (Bandelow et al., 2012; Bauer et al., 2015). 45.6% of our patients had 6 or more prescriptions, allowing us to infer

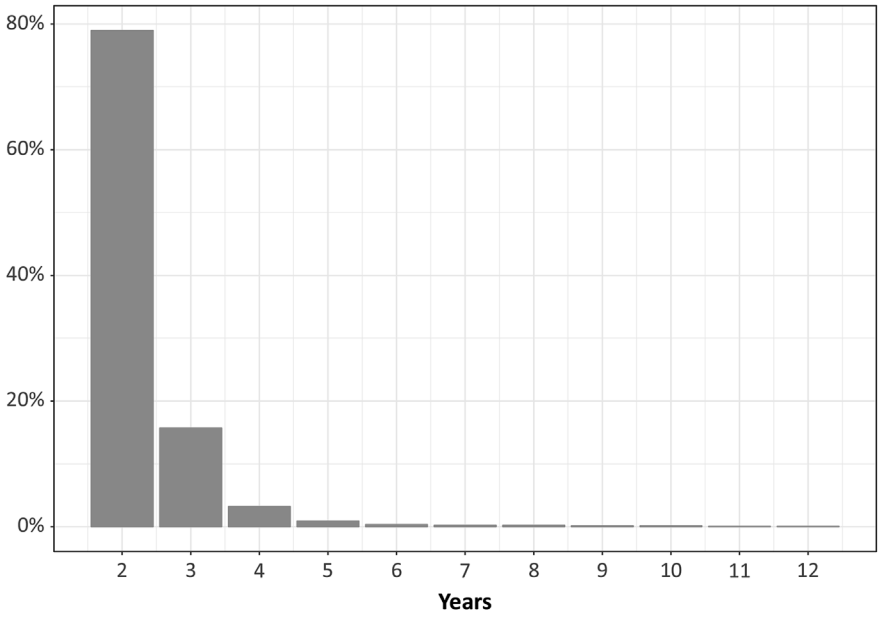

Fig. 2. Percentage of SAD-med patients fulfilling the definition of SAD-med by number of years.

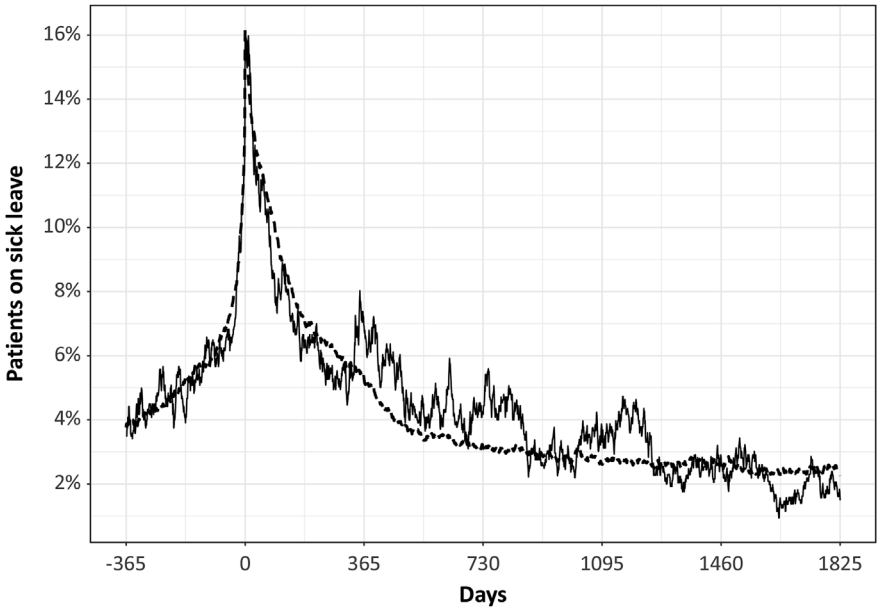

Fig. 3. Percentage of patients on sick leave starting from 1 year (day −365) prior to the first prescription of an antidepressant (day 0) to 5 years (day 1825) afterwards. SAD-med patients are presented with a solid line and non-SAD patients with a dashed line. A distinctive seasonal pattern was identified in SAD-med patients.

that more than half of patients might not be treated according to the guidelines. Different reasons on part of the health system, the medical doctors, and the patients might be implicated in this phenomenon.

The 10-year prevalence of SAD according to the DSM-5 (American Psychiatric Association, 2013) in the general population of Austria has been reported to be as high as 2.5% (Pjrek et al., 2016). Our findings showed seasonal prescriptions as surrogate marker for treated SAD in 0.74% (mean 10 year prevalence for SAD-med in insured cases). If SAD-med were a perfect match with the DSM-5 definition of SAD, this would indicate that nearly 30% of SAD patients would receive antidepressant treatment at some time point. However, the number of years with seasonal treatment (i. e. the stability of the definition) was low in SAD-med patients, which might be due to the generally low adherence to medication or to antidepressants being only second line for SAD patients beside other treatments (e. g. light therapy). As this is the first study using seasonal antidepressant prescriptions as a surrogate marker for the prevalence of SAD, its validity and usefulness are unknown at the moment. Future studies will have to work on further characterization of SAD-med or similar surrogate markers.

Between 2004 and 2016 the mean number of sick leaves in the Austrian working population was 12.7 days per year (Statistik Austria, 2016). Within the observation time frame of −1 year before prescription to 5 years afterwards patients with antidepressant prescriptions in our sample had 37.8% more sick leave days. This figure strongly depends on the reference period and restriction of the time frame of observation around the prescription date results in far higher numbers.

Subgroup analysis of sick leave levels showed that males had higher sick leave days per year than females in our sample as also observed in the general population of Austria (Statistik Austria, 2016). A statistically significant difference between SAD-med and non-SAD was found, but the values of the two groups are numerically quite similar. This leads us to conclude that in terms of sick leaves SAD-med patients are no less sick than patients of the non-SAD group. In this context it would be interesting to explore a possible association between sick leave levels in SAD and psychopathological as well as personality factors that have been found to prevail in the disorder (Bagby et al., 1996; Gordon et al.,

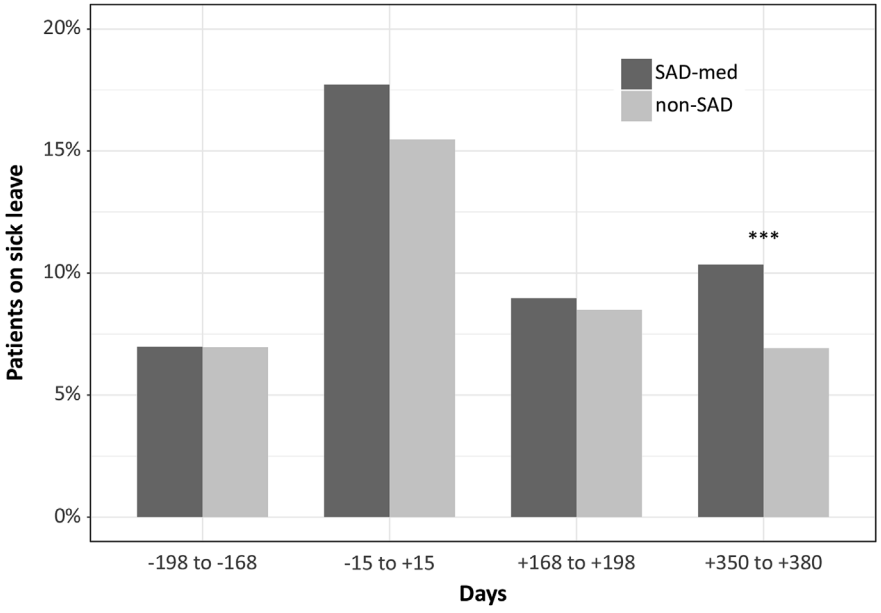

Fig. 4. Percentage of SAD-med and non-SAD patients on sick leave during 4 a priori defined 30 day time periods: 1. half a year before antidepressant prescription (day −198 to −168), 2. around the first antidepressant prescription (day −15 to +15), 3. half a year later (day +168 to +198), and 4. one year later (day +350 to +380). ***p < 0.0001 between SAD-med and non-SAD group.

1999; Jang et al., 1997). Our analysis provides strong evidence for seasonality in sick leaves in SAD-med, while this feature is lacking in the non-SAD group. This is particularly important from a socio-economic point of view, because the predictable and recurrent nature of SAD makes it especially well-suited for preventative treatment (Nussbaumer-Streit et al., 2017, 2018).

We could assume that the use of antidepressants leads to a decrease of sick leaves, but such a simple relationship cannot be derived from our data. The sick leave curve over time (Fig. 3) has a particular shape with a sharp increase during the last weeks before initial prescription and a more gradual decline afterwards. Nevertheless, return to baseline levels is slow and takes at least one year in non-SAD patients (in the SAD-med group sick leave levels peak again after one year). We can hypothesize that it is the increasing dynamics of the illness that leads to patients being signed off sick by their medical doctors shortly before or after the prescription of an antidepressant. A similar observation of a close link between sick leaves and antidepressant prescriptions has already been made by Gasse et al. (2013) in a Danish cohort study. However, in contrast to their study our present analysis was based on an even larger sample also including short-term sick leaves. The peak of sick leaves at initial prescription is produced by synchronization of the prescription date as day zero. The gradual decline over time after the initial prescription in the non-SAD group is not only due to clinical improvement of the patients but also due to patients having recurrent episodes at different time points and coming out of sync, whereas SAD-med patients are by definition synchronized with the seasons for at least two years.

Our approach might be limited by including patients with seasonal prescriptions for indications other than SAD (e. g. seasonal psychosocial stress). Moreover, SAD patients, who only received treatment with an antidepressant once, would be found in the non-SAD group in this study. Finally, SAD patients with further prescriptions of antidepressants during the summer period after initiation of treatment during the previous fall-winter period were not detectable by our definition of SAD-med.

In this large study population, we were able to show that antidepressant prescriptions are regularly preceded and followed by increases of sick leaves, which lead to overall higher sick leave levels compared to the general population. In patients with seasonal recurrence of antidepressant treatment (3% of patients with an antidepressant prescription) also the sick leaves show a recurrence during the next years. Patients with seasonally recurring prescriptions experience similar sick leave levels than patients with no seasonality. What we cannot learn from our study is what happens to patients with seasonal prescriptions, when they stop to take antidepressants. How many remit or relapse or develop another disorder? How many receive non-pharmacological treatments? These clinically meaningful and still unresolved issues might encourage researchers to longitudinally investigate the treatment paths of those patients.

Statement of interest

SK received grants/research support, consulting fees and/or honoraria within the last three years from Angelini, AOP Orphan, AstraZeneca, Celegne, Eli Lilly, Janssen-Cilag, KRKA, Lundbeck, Neuraxpharm, Pfizer, Pierre Fabre, Schwabe, and Servier. GK received travel grants from Roche, Pfizer, and AOP Orphan. DW received lecture fees/authorship honoraria from Angelini, Lundbeck, and Medizin Medien Austria. The other authors report no financial or other relationship possibly relevant to the subject of this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.01.020.

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