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The frequency of hospitalizations prior to and after conversion to a rebate pharmaceutical in depression patients in Germany

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Abstract. Background: The aim of this study was to investigate the frequency of hospitalization in depression patients with and without conversion to a rebate pharmaceutical and to show the negative consequences of rebate contracts on the health of patients with depression. Methods: This retrospective study was performed using two databases that included data on ~ 10 millions patients gathered between July 2009 and June 2012. This study included adults (> 18 years) on an antidepressive drug therapy who had statutory health insurance with rebate contracts on antidepressive pharmaceuticals. Results: In total, 47,968 patients on an antidepressive drug therapy were included in the persistence analysis using the IMS Disease Analyzer database. Of those, 26,651 patients were converted to a rebate product whereas 21,317 patients continued with the initial pharmaceutical product. After adjusting for the majority of demographic and clinical variables, the risk of hospitalization was 57% higher in patients who switched to a rebate pharmaceutical in comparison to patients who did not. When projected to the national level, this was found to equal an additional 34,157 patients hospitalized due to conversion to a rebate pharmaceutical resulting in direct inpatient costs amounting to 363.8 million EUR per year in Germany. Conclusions: Despite some limitations, this analysis presents a clear association between the initiation of rebate contracts and a negative impact on the health of patients on an antidepressive drug therapy.

Introduction

The Act on the Stabilization of Contributions to Statutory Health Insurers ("Beitragssicherungsgesetz") came into force in January 2003 and set the compulsory conditions for rebate contracts. The options for statutory health insurance companies regarding the composition of rebate contracts were refined by the Economic Optimization of Pharmaceutical Care Act ("Arzneimittelversorgungs-Wirtschaftlichkeitsgesetz"), which came into effect in May 2006, and the health system reform bill ("GKV-Wettbewerbsstärkungsgesetz"). The health system reform bill became operative in April 2007 and allowed for the realization and initiation of rebate contracts, which have been used by many statutory health insurance companies. The German Federal Government aims to lower the costs of pharmaceutical products for statutory health insurance companies through rebate contracts.

The large number of rebate contracts alongside the unavailability of and frequent switches between pharmaceutical products leaves many patients insecure [1]. According to a statement by the Allensbach Institute, every third German receives a different pharmaceutical product than that prescribed by their physician or from what the patient was familiar with before the initiation of rebate contracts [2]. Furthermore, 7% of the affected patients and 11% of those over 60 years old stated having problems, especially with tolerance and side effects, associated with a pharmaceutical product due to the rebate contract switch. Moreover, impairment of the therapeutic effect was mentioned by patients. However, for some pharmaceuticals, i.e., antidepressive drugs, the substitution specified by the German Pharmaceutical Society ("Deutsche Pharmazeutische Gesellschaft") is especially critical given that the accurate adjustment of medicines is essential

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to therapeutic success and the avoidance of side effects [3].

A questionnaire created with general practitioners (GPs) in Germany about their experiences with rebate contracts showed that most GPs have significant problems with switched drugs due to the discount contracts. A high percentage of the respondents noticed a significant impairment in patient compliance and the doctor-patient relationship [4].

Non-compliance is fundamental in pharmaceutical therapy. Studies reveal that every fifth prescription is not honored at the pharmacy level (primary non-compliance) and that non-compliance is present in 50% of prescribed pharmaceutical products. Even life-saving drugs are not excluded, as the compliance rates for statins in the secondary prevention of myocardial infarction and stroke prove [5].

Non-compliance is often followed by therapeutic failure and significant costs to the health care system and society. In the case of antibiotics, non-compliance leads to therapeutic failure, an increase in the incidence of relapse, the development of resistance, and higher rates of complications. In addition, the extension of disease duration results in significant economic costs [6]. Therapeutic failure and the associated consequences including the aggravation of disease can lead to excessive physician visits and additional examinations, prescriptions, hospitalizations, and the associated direct and indirect costs [7].

In our article published in 2010, we demonstrated that rebate contracts were associated with a worsening persistence and higher therapeutic withdrawal rates in patients on an antidepressive drug therapy [8]. Additional resources were expended on patients who switched to a rebate product, primarily due to higher rates of hospitalization. Direct and indirect costs were estimated to amount to 23 million EUR due to additional hospitalization rates within the first year after therapy conversion [8]. However, this study focused on patients who were treated between 2007 and 2009, soon after rebate contracts were initiated. The aim of the present study was to investigate the frequency of hospitalization in depression patients with and without conversion to a rebate pharmaceutical based on newer epidemiological data in order to confirm the earlier results.

Methods

Databases

This retrospective analysis was performed combining two databases: the IMS Contract Monitor® and the IMS Disease Analyzer®.

The IMS Contract Monitor® database contains information regarding the volume of drugs delivered via public pharmacies in the statutory health insurance market at the national level. It is differentiated according to the seven individual state health insurance types and identifies the five largest substitute sickness insurance societies in the SHI market. The designation is compliant with § 305a SGB V (Social Security Code Book V) and takes into account discount agreements pursuant to § 130a para. 8 SGB V. The data contain an identification of the rebate regulated commercial forms. Based on the IMS Contract Monitor®, information concerning the drug manufacturer, the health insurance involved in the discount contracts, and the introduction date of a discount contract (that is, the index date in the group of patients who were not switched to a discount drug) can be determined.

The IMS® Disease Analyzer database contains data from Germany, the UK and France and allows anonymous access to a select panel of physicians' practices and patients. The data are generated directly from computers in physicians' offices via a standardized interface and provide daily routine information on patients' diseases and therapies. A physician's practice transmits patient data stored in the physician's computer to IMS on a monthly basis. Before transmission, the data are encrypted for protection and contain in a comparable format and level of detail information from the patient files in the doctor's practice. Each month the physician receives a feedback report reflecting his/her own prescription pattern and a comparison to those of collaborating colleagues in the IMS panel within that specialty. Altogether, the database contains data from 2,351 practices and ~ 20 million German patients from January 2000 to October 2012. In addition to data from general practitioners and specialists in internal medicine, data for various specialist groups are also recorded in Germany. The Disease Analyzer database provides a complete listing

Table 1. Baseline characteristics of the study patients.

Variable	Switch (n = 26,651)	No switch (n = 21,317)
Mean age (standard deviation)	61.0 (15.3)	61.1 (15.0)
Female patients in %	69.8	70.6
Western Germany in %	79.3*	75.6*
Neurological/psychiatric practice in %	55.0*	53.2*
Endocrine, nutritional and metabolic diseases (ICD 10: E00-E90)	37.9*	38.8*
Diseases of the circulatory system (ICD 10: I00-I99)	45.0	45.7
Diseases of the digestive system (ICD 10: K00-K93)	33.6	34.4
Diseases of the genitourinary system (ICD 10: N00-N99)	25.6	25.2
Neoplasms (ICD 10: C00-D48)	20.0	19.6

*p-value < 0.05.

of all relevant patient details for each practice. The data obtained directly from practices are checked for plausibility, linked to relevant additional information such as the price of a pharmaceutical product, ATC and ICD coded, saved, and updated on a monthly basis. The data bank includes only anonymized data in compliance with the regulations of the applicable data protection laws. The sampling method for the Disease Analyzer database is based on summary statistics from all doctors in Germany published yearly by the German Medical Association ("Bundesärztekammer"; http://www.baek.de). The statistical unit of IMS uses these statistics to determine the panel design according to the following strata: specialist group, German federal state, community size and age of physician. This panel design forms the basis for the acquisition of the practices processed in the Disease Analyzer. Technical support and setup within participating practices is carried out by cooperating software companies using a standardized interface designed for IMS that enables each practice to collect the required data and send them to IMS in an anonymized format [9, 10].

The validity of the Disease Analyzer data was previously evaluated and described [11]. It has been the object of a number of studies and peer-reviewed scientific publications in the fields of epidemiology and health economics as well as in depression [12, 13].

Study population

Initial prescription of a rebate antidepressant (ATC: N06A) between July 2009 and June 2011 in subjects diagnosed with depression (ICD 10: F32, F33) were defined as the index dates. Patients with a follow-up visit of less than 365 days prior to the index or less than 365 days after the index date were excluded. This exclusion was necessary for the correct identification of hospitalization frequency prior to and after the index date. Further inclusion criterion included age at the index date above 18 years.

In total, 47,968 patients were included in this study (25,987 in neurological or psychiatric practices and 21,981 in general practices). These patients were treated in 162 neurological or psychiatric centers and 791 general practices. From the total, 26,651 (55.6%) patients were converted to a rebate pharmaceutical.

Outcome parameters

Hospitalization rates due to depression within 1 year of the index date were compared to hospitalization rates prior to the index date. The association between hospitalization rates and conversion to a rebate product was analyzed using multivariate regression adjusting for potential confounders (age, gender, insurance status, region, co-diagnoses and co-therapies). Direct costs due to the additional hospitalization of patients who were switched to a rebate product were estimated based on an official source [14].

Results

Study population

In total, 47,968 patients on an antidepressive drug therapy were included in the

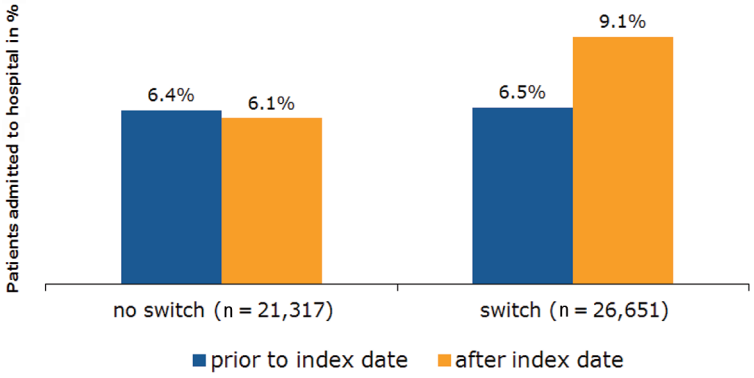

Figure 1. The percentage of hospital admissions among patients with and without switch to a discounted antidepressant.

persistence analysis using the Disease Analyzer database. We found that 26,651 patients were converted to a rebate product whereas 21,317 patients continued with the initial pharmaceutical product. The demographic characteristics of study patients are shown in Table 1. Mean age was nearly the same in both groups. The proportion of patients living in Western Germany was significantly higher in the group who were switched to a rebate pharmaceutical. Patients who were switched to a rebate product were seen slightly more often in neurological practices. There were no differences between groups in recorded co-diagnoses.

Frequency of hospitalizations (descriptive analysis)

The descriptive analysis shows that patients who switched to a rebate product required further hospitalizations, whereas the proportion of patients who remained on their initial therapy requiring hospitalization remained stable or decreased. In patients who did not switch, 6.4% were admitted into hospital within 12 months prior to the index date and 6.1% within 12 months after the index date. In patients who switched, 6.5% were admitted to hospital prior to the index date, while 9.1% were admitted after the index date ($p < 0.001$) (Figure 1). The proportion of patients admitted to hospital prior to and after the switch to a rebate antidepressant was higher in patients 65 years and older than in patients younger than 65 ($p < 0.001$) and higher in male patients than in female patients ($p < 0.001$) (Figure 2).

Probability of hospitalization (regression analysis)

The unadjusted probability of hospitalization due to a depressive episode in depression patients was 54% higher after a switch to a rebate pharmaceutical compared to patients who remained on the initial therapy

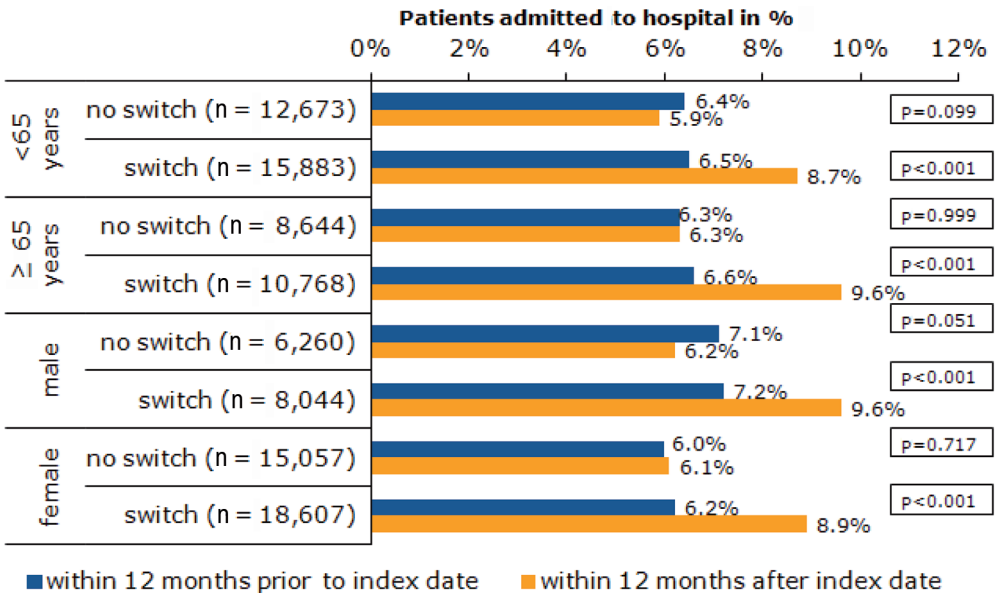

Figure 2. The percentage of hospital admissions among patients with and without switch to a discounted antidepressant by age and sex.

Table 2. Probability of admission into hospital for antidepressant patients after switching to a discounted product.

Logistic regression model	Odds ratio (95% CI)	p-value
Without covariates	1.54 (1.44 – 1.65)	< 0.001
Adjusted for hospitalization prior to index date	1.56 (1.45 – 1.67)	< 0.001
Adjusted for hospitalization prior to index date, age, gender, and region	1.55 (1.44 – 1.66)	< 0.001
Adjusted for hospitalization prior to index date, age, gender, region, and co-morbidities	1.57 (1.46 – 1.68)	< 0.001

Table 3. Probability of admission into hospital for depression patients after switching to a discounted product in different patient groups.

Patient group	Odds ratio (95% CI)*	p-value
Patients younger than 65	1.53 (1.40 – 1.68)	< 0.001
Patients 65 years and older	1.60 (1.44 – 1.79)	< 0.001
Male patients	1.65 (1.45 – 1.89)	< 0.001
Female patients	1.53 (1.40 – 1.67)	< 0.001
Western Germany	1.62 (1.50 – 1.76)	< 0.001
Eastern Germany	1.38 (1.18 – 1.62)	< 0.001
General practices	1.66 (1.52 – 1.81)	< 0.001
Neurological practices	1.48 (1.31 – 1.67)	< 0.001

*adjusted for hospitalization prior to index date, age, gender, region, and co-morbidities.

($p < 0.001$). After adjusting for the majority of demographic and clinical variables, the risk of hospitalization was 57% higher in patients who switched to a rebate pharmaceutical in comparison to patients without a change in their drug therapy (Table 2). Moreover, in patients over 65 years, this risk of hospitalization was 60%, 65% in male patients, 62% in Western Germany, and 66% and higher in patients treated in a general practice (Table 3).

Hospitalization costs

Costs to the German health care system have mounted, particularly due to frequent hospitalizations. The costs associated with additional hospitalizations in patients who converted to a rebate pharmaceutical were determined as the percentage of depression patients who were switched to a rebate pharmaceutical and hospitalized (that is, 103,609 patients). In contrast, only 69,452 patients who did not switch to a rebate would have been hospitalized within 1 year of therapeutic conversion. Thus, 34,157 additional patients would be hospitalized due to the conversion to a rebate pharmaceutical. Based on a mean inpatient stay of 50 days and a mean cost of 10,650 EUR per hospitalization reported in Stamm et al. [14], the direct inpatient costs amount to 363.8 million EUR per year in Germany. Indirect costs and additional non-productive days due to illness were not considered.

Discussion

The results of this analysis reveal that rebate contracts are associated with a higher frequency of hospitalizations in patients on an antidepressive drug therapy. This may be interpreted as a result of patient irritation due to the rebate pharmaceutical or may be a consequence of problems associated with the medication, such as adverse events or a decreased effectiveness.

The goal of the treatment of depression is remission, meaning the complete or near-complete resolution of all symptoms [15]. Ideally, treatment of depression should be continued for a minimum of 12 months after remission. The dose of the antidepressant used during the period following remission should be the same as that used during the acute phase [16]. Continued treatment with antidepressants would benefit many patients with a recurrent depressive disorder [17]. However, antidepressants are known to have a very poor compliance rate. Approximately 4 out of 10 adults who initiate antidepressant therapy for the treatment of depression discontinue their medications during the first month of treatment. Often, side effects are important determinants of premature antidepressant discontinuation [18]. Many patients with depression do not respond to the first antidepressant they are prescribed and switch to another. This changeover period is a high-risk time for discontinuation reactions as well as drug interactions [19]. In cases when patients interrupt antidepressant

therapy, discontinuation symptoms occur with all classes of therapies including dizziness, headache, nausea and lethargy or electroshock-like sensations. In most patients, discontinuation symptoms are of a short duration and mild, although in some cases they can be severe, last several weeks and cause significant morbidity [20].

Switches to a rebate antidepressant have clinical as well as "economic" reasons. But, such changes in therapy follow abrupt stoppage rather than the tapering of antidepressants at the end of treatment. Persistence analysis showed that depressive patients who were converted to a rebate product had a higher rate of therapy withdrawal compared to patients without conversion. The proportion of converted depression patients who withdrew from therapy within 3 months after the switch was 48.1% higher than the proportion of patients who discontinued treatment within the same period and were receiving the initial drug therapy [8]. Resource utilization was increased in patients who switched to a rebate product, especially given the higher rates of hospitalization. Direct costs were estimated to reach 364 million EUR due to additional hospitalization rates within the 1st year after therapy conversion. This number is based on only one diagnosis and only associated with hospitalization costs, and would be much higher with the inclusion of other diagnoses and other costs. In addition, this figure could be better evaluated if compared to the total savings made possible through the rebate contracts. According to figures released by the Department of Health, a total of 1.6 billion EUR were saved in 2011 by means of rebate contracts [21].

Several studies indicate non-compliance due to a switch to another pharmaceutical product in patients other than those with depression [4, 22, 23, 24]. Often, patients feel irritated by their medication, and errors in drug application and dosing are seen [22]. The majority of patients who convert to a rebate product experience adverse events due to the new drugs or report serious problems regarding medication intake [4]. However, massive pressure on physicians due to rebate contracts was reported [23, 24].

Fundamental limitations in the data should be kept in mind when interpreting the results of this study. This analysis was conducted to evaluate the impact of rebate contracts on the health of patients on an antidepressive drug therapy and should not be interpreted beyond that. The mean inpatient stay and the mean costs of a hospital stay were estimated based on a study including ten hospitals in Bavaria, Baden-Wuerttemberg and Nordrhein-Westfalen carried out between 2001 and 2003. The actual costs may vary. However, this study made use of the best available evidence. Furthermore, the effectiveness of a therapy could not be analyzed given that relevant outcome parameters were not documented in the database (i.e., suicides).

Despite the above limitations, this analysis presents a clear association between the initiation of rebate contracts and a negative impact on the health of patients on an antidepressive drug therapy. The impact of rebate contracts on the health of patients and the health care costs should be evaluated in further therapeutic fields through additional research projects.

Conflict of interest

There are no declarable financial or other relationships

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