Which adverse effects influence the dropout rate in selective serotonin reuptake inhibitor (SSRI) treatment? Results for 50,824 patients

Welche unerwünschten Ereignisse haben einen Einfluss auf die Behandlungsabbruchrate von selektiven Serotonin-Wiederaufnahmehemmern (SSRI)? Ergebnis von 50.824 Patienten

Abstract

Background: Nowadays, selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed antidepressants due to their superior clinical efficacy, effectiveness, tolerability, and safety as compared to tricyclic antidepressants or monoamino oxidase inhibitors. However, despite these advantages SSRIs are still associated with a number of adverse drug reactions, especially in the early stages of treatment, which may lead to premature discontinuation of therapy in some cases. The aim of the present study was to assess the most common adverse drug reactions of SSRIs as well as their impact on dropout rate in a large study population.

Patients and methods: Data for 50,824 patients treated for major depressive disorder with SSRIs for the first time was accessed via the Disease Analyzer database (IMS Health, Germany), providing information on SSRI adverse drug reactions and their influence on premature treatment discontinuation calculated by regression analysis. The presence of certain co-morbidities was also registered.

Results: The mean age was 54.5 ± 19 years, two-thirds of the study population being female. The adverse effects mentioned most frequently were: "discomfort" of the digestive system (10%), sleep disorders (8.6%), and heart rhythm disorders (4%); however, these were of tolerable severity as they did not significantly influence the dropout rate. Contrary to that, somnolence and younger age (≤50 years) in particular increased the chance of premature treatment discontinuation, while patients suffering from cardiovascular risk factors or osteoporosis tended to adhere to the therapy.

Conclusions: Overall, there is high tolerability for early SSRI treatment, whereas the occurrence of somnolence leads to discontinuation.

Keywords: antidepressants, selective serotonin reuptake inhibitors, adverse drug reactions, dropout

Karel Kostev[1]
Juliana Rex[1]
Thilo Eith[2]
Christina Heilmaier[3]

1 IMS Health, Frankfurt, Germany

2 Fresenius University of Applied Sciences, Idstein, Germany

3 FOM University of Applied Sciences, Essen, Germany

Zusammenfassung

Hintergrund: Heutzutage sind Serotonin-Wiederaufnahmehemmer (SSRI) aufgrund ihrer verglichen mit trizyklischen Antidepressiva oder Monoamino-Oxidase-Inhibitoren überlegenen klinischen Wirksamkeit, Verträglichkeit und Sicherheit die meistverschriebenen Antidepressiva. Dennoch sind trotz dieser Vorteile SSRIs mit einer Vielzahl an unerwünschten Arzneimittelnebenwirkungen verbunden, insbesondere im frühen Stadium der Behandlung, was in manchen Fällen zu einem verfrühtem Therapieabbruch führen kann. Das Ziel der vorliegenden Studie war es die meisten unerwünschten Arzneimittelnebenwirkungen von SSRIs zu erfassen sowie die Auswirkung auf die Behandlungsabbruchrate in einer großen Population zu ermitteln.

Patienten und Methoden: Daten von 50.824 Patienten mit einer SSRI-Erstbehandlung einer schweren depressiven Störung wurden über die IMS (R) Disease Analyzer Datenbank (IMS Health) retrospektiv analysiert, wobei Informationen über unerwünschte SSRI-Nebenwirkungen und deren Einfluss auf einen verfrühten Therapieabbruch über Regressionsanalysen ermittelt wurden. Das Auftreten von bestimmten Co-Morbiditäten wurden ebenfalls registriert.

Ergebnisse: Das mittlere Alter war 54.5 (±19) Jahre, zwei Drittel der Population waren weiblich. Die meist dokumentierten unerwünschten Nebenwirkungen waren: Beschwerden des Verdauungssystems (10%), Schlafstörung (8.6%) und Herzrhythmusstörung (4%); diese waren allerdings von erträglichem Ausmaß, da dadurch die Drop-Out-Rate nicht signifikant beeinflusst wurde. Hingegen erhöht insbesondere Somnolenz als Nebenwirkung und jüngeres Alter (≤50 Jahre) die Wahrscheinlichkeit eines vorzeitigen Therapieabbruchs, während Patienten mit kardiovaskulären Risikofaktoren oder Osteoporose die Tendenz aufweisen die Therapie aufrechtzuerhalten.

Schlussfolgerung: Insgesamt wurde eine gute Verträglichkeit der SSRI-Behandlung nachgewiesen, wohingegen das Auftreten von Somnolenz zu einem Therapieabbruch führte.

Schlüsselwörter: Antidepressiva, selektive Serotonin-Wiederaufnahmehemmer, unerwünschte Arzneimittelnebenwirkungen, Drop-Out-Rate, Behandlungsabbruch

Introduction

Nowadays, antidepressants are one of the most frequently prescribed drugs worldwide with the class of selective serotonin [5-hydroxytryptamine (5-HT)] reuptake inhibitors (SSRIs) now established as the most commonly purchased since their introduction in the late 1980s [1], [2]. Leading SSRIs include citalopram (Celexa®), fluoxetine (Prozac®), paroxetine (Paxil®) or sertraline (Zoloft®). They are considered mainstays in the treatment of major depressive disorder and some of them are also approved for the treatment of conditions such as panic disorder, anxiety disorder or posttraumatic stress disorder [2].

Changes in neurotransmitter activity, such as reduced levels of serotonin or noradrenalin, may lead to the development of depression. SSRIs work by selectively blocking the presynaptic reuptake of serotonin in the brain stem and spinal cord [2], [3], thereby making more serotonin available, which in turn improves mood and behavior. In addition to their clinical efficacy and effectiveness, SSRIs have exhibited better levels of tolerability and safety than the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOs) [4] used to date, which is probably due to their lower affinity toward other neurotransmitter systems such as α-1 adrenergic, muscarinic or histaminergic receptors or fast sodium channels that are affected by TCAs [2]. These advantages include fewer anticholinergic effects, a better cardiovascular profile, ease of use and lower risk in case of overdose [2]. Nevertheless, some adverse drug reactions can arise during SSRI treatment, which may ultimately lead to treatment discontinuation. These adverse effects include nausea, diarrhea, headache, insomnia, nervousness, tachycardia or weight gain, with severity varying considerably among the different SSRIs as shown in a meta-analysis published in "The Lancet" [5]. This is due to differences in pharmacological characteristics such as variable potency of the SSRIs as inhibitors of the specific cytochrome-P450 (CYP)-enzymes [6], [7], their plasma protein binding capability [8] or different half-lives [8], all influencing the likelihood of clinically significant drug-drug interactions. Sertraline and citalopram, for example, have the lowest risk of enzyme inhibition, while fluoxetine is linked with a high chance of drug interaction.

The aim of the present study was to assess the most common adverse drug reactions occurring within 30 days after first prescription of SSRIs ("index date") as well as their impact on dropout rate in a large study population of more than 50,000 patients above 18 years of age.

Patients and methods

Disease Analyzer database

The Disease Analyzer database (IMS HEALTH) compiles drug prescriptions, diagnoses, and basic medical and demographic data obtained directly from the computer systems from the practices of general practitioners and specialists throughout Germany [9]. Diagnoses (ICD-10), prescriptions (Anatomical Therapeutic Chemical (ATC) Classification System), and the quality of reported data are monitored continuously by IMS on the basis of a number of quality criteria (e.g., completeness of documentation, linkage of diagnoses and prescriptions, etc.). The data are generated directly from the computers in physicians' practices via standardized interfaces and provide daily routine information on patient diseases and

therapies. Each practice transmits patient data stored on the physician's computer to IMS on a monthly basis. Before transmission, the data are encrypted for data protection purposes. The validity of the Disease Analyzer data has already been evaluated and described [9], [10]. The analysis of physicians' age and regional distributions among participating practices showed that the selection appears to be representative of the general physician population [10]. Further analysis indicated that the distribution of patients by health insurance fund in Disease Analyzer was very similar to the overall distribution of patients by health insurance fund in Germany [10]. Different comparisons were also performed for diabetic medication or incidence of cancer diagnoses which were in line in statistics from Robert-Koch-Institute [10]. It has formed the basis of a number of studies and peer-reviewed scientific publications in the fields of epidemiology and drug safety research [11], [12].

Study population

First-time prescriptions of SSRI (ATC: N06A4) from January 2009 until December 2012 in subjects diagnosed with depression (ICD 10: F32, F33) were defined as the index dates; the latest follow-up date was identified as December 2013.

Patients with a follow-up time of less than 365 days prior to the index date were excluded. This exclusion was necessary for the correct determination of treatment initiation. Age of above 18 years formed another inclusion criterion. We excluded children and adolescents from our study because they have developmentally different pharmacodynamics and pharmacokinetics compared to adults, which impacts adverse drug reactions [13] and would distort analysis. A total of 50,824 patients were available for therapy discontinuation analysis. These patients were treated in 1,192 general practices.

Study outcomes

The first outcome measure was the share of patients with defined adverse drug effects within 30 days of initial prescription of SSRI. As adverse drug reactions usually occur in first days after therapy start, the duration of 30 days was elected. The following adverse drug reactions were defined based on ICD 10 classification: symptoms and signs involving the digestive system and abdomen (R10–19), sleep disorders (G47), heart rhythm disorders (I45–49), dizziness (R42), malaise and fatigue (R53), headache (R51), symptoms and signs concerning food and fluid intake (R63), hyperhidrosis (R61), sexual dysfunctions (F52), gastrointestinal hemorrhage (K92.2), somnolence (R40.0) and further unspecified adverse effects (T88.7).

The impact of these adverse drug reactions on the discontinuation of SSRI treatment was also investigated. Treatment discontinuation was defined as the absence of the second SSRI prescription or a switch to another anti-depressant class (monoamine reuptake inhibitors, monoamine oxidase inhibitors or other antidepressants).

Covariates

Demographic data included age, gender, health insurance status (private or statutory), and practice region (Eastern versus Western Germany). Co-diagnoses were determined based on primary care diagnoses for mental and behavioral disorders due to the use of psychoactive substances (F10–19), anxiety, dissociative, stress-related, somatoform disorders (F40–48), diabetes (E10–14), hypertension (I10), hyperlipidemia (E78), coronary heart disease (I24–25), cancer (C00–99), asthma (J45–46) and osteoporosis (M80–81).

In addition, the Charlson Comorbidity Index (CCI) was used as general marker for co-morbidity. This is a weighted index that accounts for the number and severity of comorbidities (e.g. myocardial infarction, diabetes, stroke or heart failure) in administrative database studies [14] and helps to decide how aggressively to treat a condition.

Statistical analysis

A logistic regression model was used to estimate the relationship between therapy discontinuation and the adverse drug reactions. A stepwise selection procedure with the entry criterion $p<0.05$ was used to select the final optimal model. The adjusted odds ratios (OR) and 95% confidence intervals (CI) are presented for the independent variables.

Potential confounders (age, gender, private health insurance, region and co-diagnoses) were included as independent variables. Two-sided tests were used and a p value of less than 0.05 was considered statistically significant. All analyses were carried out using SAS 9.3 (SAS Institute, Cary, USA).

Results

Patient characteristics and comorbidities

Data from a total of 50,824 patients attending 1,192 general practices were available for analysis. The mean age was 54.5 ± 19 years with 45% of patients ≤50 years old, two-thirds of the study population were female, 6.2% had private health insurance and 90.6% lived in the Western area of Germany (Table 1). Table 2 also provides a survey on the presence of certain comorbidities with anxiety, dissociative, stress-related, and somatoform disorders (F40–48; 31.4%) or cardiovascular risk factors such as hypertension (I10; 31.7%), hyperlipidemia (E78; 14%) or diabetes (E10–14; 11%) being the most frequent. The mean Charlson Comorbidity Index (CCI) was 1.3 ± 1.0, indicating that most patients suffered from 1 or 2 comorbidities.

Table 1: Baseline characteristics of study patients

Variable	Value	Variable	Value
N	50,824	Charlson comorbidity score (Mean, StD)	1.3 (1.0)
Age (Mean, StD)	54.5 (19.0)	Dementia (%)	3.7
Age ≤40 (%)	24.8	Mental and behavioral disorders due to psychoactive substance use (F10–19) (%)	5.2
Age 41–50 (%)	20.1	Anxiety, dissociative, stress-related, somatoform disorders (F40–48) (%)	31.4
Age 51–60 (%)	18.4	Diabetes (E10–14) (%)	11.0
Age 61–70 (%)	11.7	Hypertension (I10) (%)	31.7%
Age 71–80 (%)	13.7	Lipid metabolism (E78) (%)	14.0%
Age ≥80 (%)	11.3	Coronary heart disease (I24–25) (%)	7.3%
Male gender (%)	32.5	Cancer (C00–C99) (%)	5.2%
Private health insurance (%)	6.2	Asthma (J45–46) (%)	4.8%
Western Germany (%)	90.6	Osteoporosis (M80–81) (%)	4.3%

Table 2: Documented adverse drug reactions occurring during therapy with SSRIs

Adverse drug reactions (ICD 10-code)	Number and share of patients
Symptoms and signs involving the digestive system and abdomen (R10–19)	5,082 (10.0%)
Sleep disorders (G47)	4,382 (8.6%)
Heart rhythm disorders (I45-49)	2,011 (4.0%)
Dizziness (R42)	1,838 (3.6%)
Malaise and fatigue (R53)	1,798 (3.5%)
Headache (R51)	1,526 (3.0%)
Symptoms and signs concerning food and fluid intake (R63)	760 (1.5%)
Hyperhidrosis (R61)	313 (0.6%)
Sexual dysfunctions (F52)	239 (0.5%)
Gastrointestinal hemorrhage (K92.2)	230 (0.5%)
Somnolence (R40.0)	71 (0.1%)
Unspecified adverse effects (T88.7)	571 (1.1%)

Adverse drug reactions occurring during SSRI treatment

Analysis of the adverse drug reactions arising during SSRI treatment showed that 10% of patients suffered from symptoms and signs involving the digestive system and abdomen (R10–19), 8.6% exhibited signs of sleep disorders (G47), and heart rhythm disorders occurred in 4%. Other, less frequently encountered, adverse effects are listed in Table 2.

Cox regression analyses revealed that somnolence was by far the most frequently cited reason for discontinuation of SSRI treatment (OR: 8.42; 95% CI: 1.86–38.10). Other factors that positively influenced the dropout rate were headache (OR: 1.32; 1.05–1.66), younger age (≤40 years) (OR: 1.19; 1.12–1.26) or male gender (OR: 1.09; 1.05–1.13), while the presence of dementia, hypertension or hyperlipidemia was associated with the continuation of SSRI treatment to a significant extent (Table 3) (all $p<0.05$).

Table 3: Cox regression analyses related association of SSRI treatment discontinuation after first prescription with defined outcomes

Outcome variables	Odds ratio (95% CI)	p-value
Adverse effects: somnolence	8.42 (1.86–38.10)	0.0056
Adverse effects: headache	1.32 (1.05–1.66)	0.0164
Unspecified adverse effects	1.61 (1.21–2.15)	0.0012
Age ≤40	1.19 (1.12–1.26)	<0.0001
Age 41–50	1.07 (1.01–1.13)	0.0325
Male gender	1.09 (1.05–1.13)	<0.0001
Cancer	1.12 (1.03–1.21)	0.0076
Living in Western Germany	0.92 (0.86–0.97)	0.0046
Dementia	0.77 (0.69–0.85)	<0.0001
Diabetes	0.87 (0.82–0.93)	<0.0001
Hypertension	0.87 (0.83–0.91)	<0.0001
Hyperlipidemia	0.85 (0.81–0.90)	<0.0001
Osteoporosis	0.86 (0.79–0.95)	0.0017

CI = confidence interval

Discussion

Selective serotonin reuptake inhibitors (SSRIs) are now established as the most frequently prescribed antidepressant owing to their clinical efficacy and effectiveness, high tolerability and safety [2], [5], [8]. Nevertheless, adverse effects may occur during SSRI treatment, some of which may constitute a significant public health issue due to the associated poor adherence to treatment, preterm treatment discontinuation, and considerable harm incurred, as in the case of serotonin syndrome [15] or hyponatremia [6], [16].

Accordingly, we assessed adverse effects arising during first prescription of SSRIs in a very large study group of more than 50,000 patients, providing data representative for a general adult population and not confined to a specific group (e.g. elderly patients, who inherit a known higher risk for side effects during antidepressant treatment, which may be – among other reasons – due to drug interactions [17], [18], [19] or existing comorbidities [20]). Similarly to the results presented in a report by Westenberg and Sandner [8] we found that the most common adverse drug reactions were symptoms and signs involving the digestive system and abdomen such as nausea and diarrhea, probably due to an increased availability of 5-HT in the gastrointestinal system as well as in the brain [21]. However, this adverse effect occurred considerably less often than described in previous literature (10% in our study versus 15–35% by Vaswani et al. [2]) and is generally known to be transient similar as elevation of liver enzymes, which is a recognized side effect of almost all available antidepressants (especially tricyclic antidepressants (TCAs)) [22], [23]. Furthermore, as others before us [8], we often detected sleep disorders, although evidence suggests that SSRIs generally have beneficial effects on sleep quality in persons suffering from depression [24]. Heart rhythm disorders constituted the third most commonly encountered adverse drug reaction in our study, of which tachycardia and especially long QT syndrome and Torsade de Pointes have previously been reported on [8], [25], although a recently published study did not demonstrate a higher risk of cardiac mortality in patients taking SSRIs [2]. Overall, it seems that these frequently observed adverse effects were of tolerable severity in our study population as regression analysis showed that they were not accompanied by considerably higher dropout rates.

Other adverse drug reactions that were often mentioned in other studies were only seldom seen in our study population, e.g. dizziness (3.6%), malaise and fatigue (3.5%), headache (3.0%), sexual dysfunction (0.5%) [26], [27] or somnolence (0.1%). In particular, the low incidence of sexual disorders in our population is surprising given that other studies reported rates of more than 50% [2]. However, as assumed by Trenque et al., our results are probably falsely low due to instances of underreporting in the case of adverse reactions that are considered too embarrassing to report spontaneously [28]. Another explanation may be that it takes several weeks after beginning of treatment until sexual dysfunctions manifest [2]. Furthermore, gastrointestinal hemorrhage and general bleeding risk (especially in patients that additionally have been prescribed acetylsalicylic acid [29]), both associated with short-term use of SSRIs (7–28 days) [30], were only observed in a small number of patients (0.5%) within our study population. Additionally, changes in body weight, which are often associated with a low acceptance of treatment and incompliance [8], did not play a role in our study, which can be explained by the fact that it typically takes several months before weight changes become evident.

Although somnolence occurred only in a few persons (0.1% of our study population) it was by far the most common reason for patients to stop taking SSRI, which is probably due to the fact that patients suffering from depression are often younger (almost 45% of our study population were less than 50 years old) and are therefore still working. For the same reason, any impairment of cognitive psychomotor function or headache is often considered intolerable [8], although these as well as other severe adverse effects as shown in the German drug safety program in psychiatry (AMSP) [22] are less pronounced in patients taking SSRIs than those treated with TCAs.

By contrast, the presence of dementia, osteoporosis or cardiovascular risk factors (e.g. diabetes, hypertension, hyperlipidemia) made the premature discontinuation of the drug less probable. Reasons for this may include cognitive impairment in the case of dementia or higher disease awareness in patients already suffering from cardiovascular diseases or osteoporosis, even though it was confirmed in longitudinal, cross-sectional, and prospective cohort studies that SSRIs themselves decrease bone mineral density and increase fracture risk especially in long-time users, as demonstrated by lower T-scores [31], [32]. In addition, elderly patients may have a higher threshold for changing drugs and tend to be more likely to adhere to a doctor's prescription due to a lower ambition for self-determination.

Our study has recognized limitations, which need to be addressed:

1. We registered adverse drug reactions within the first 30 days after prescription only and not in the long term. This may have impacted our results negatively, given that adverse effects in antidepressants usually diminish after a while. However, the focus of our study was not on the pure occurrence of adverse drug reactions but on their severity, and on the possibility that these might lead to the premature discontinuation of drug treatment.

2. We did not perform sub-analysis for the various members of the SSRI family, although differences exist not only with regard to the disease spectrum for which they are approved, but also regarding the nature and severity of the adverse effects they induce. This is due to serotonergic polymorphisms at the receptor and transporter level [33] as well as their sec-

ondary binding to non-serotonergic receptors [8]. This means that patients may respond differently to certain SSRIs (e.g. high rate of anorexia linked with fluoxetine but low rate linked with citalopram [34]) and also explains why SSRIs are not interchangeable or why persons having discontinued intake of one SSRI because of intolerability or non-response can be treated effectively with another [15], [35], [36].

3. Daily doses of SSRIs vary considerably, which could cause significant differences in the spectrum and severity of adverse effects experienced. In citalopram, for example, daily doses >40 mg are associated with lower risks of ventricular arrhythmia as compared to lower doses [37].

4. As there is no central system that registers the drugs prescribed to a patient by different doctors, the possibility that some patients received their follow-up prescription from another doctor and were wrongly recorded as having discontinued SSRI treatment cannot be excluded.

5. Only the presence of major depressive disorder was considered as indication for SSRI prescription, but not the severity of symptoms or suicidal ideations, which might also have influenced discontinuation of treatment.

6. Possible confounders such as intake of over-the-counter drugs such as St. John's Wort, which changes the pharmacokinetics of SSRIs by induction of CYP-enzymes [38], or the use of illicit drugs were not taken into account, although they may interact with SSRIs [39].

7. Due to the short-time observation period no relevant data on the frequency of occurrence of discontinuation syndrome after long-time use of SSRIs was available [40], which may also be a significant healthcare problem.

8. And finally we did not further assess the association of SSRI-use and suicide rate, although it is known that antidepressants may increase suicide rate at the beginning, while lower rates are detected in patients receiving SSRIs for a longer period of time [41].

In summary, our study demonstrated in the context of a large study population that the most frequently encountered adverse effects occurring during the first 30 days after SSRI prescription involved the digestive system, sleep or heart rhythm disorders, but were of tolerable severity. Contrary to this, somnolence or lower age were associated with premature discontinuation of therapy, while chronic illnesses such as dementia or osteoporosis were often linked with medication adherence. It will be the task of future research to account for differences in the pharmacodynamics and pharmacokinetics of the various SSRIs as well as for the "metabolic" signature of each individual person [42] in order to contribute to personalized drug therapy, thereby improving treatment efficacy, tolerability, and compliance.

Notes

Competing interests

The authors declare that they have no competing interests.

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Corresponding author:

Dr. Karel Kostev
IMS Health, Darmstädter Landstraße 108, 60598
Frankfurt/Main, Germany, Phone: 0049-69-66044878
kkostev@de.imshealth.com