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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

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Incidence and determinants of long-term use of antidepressants

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Abstract *Objectives*: The use of antidepressants has increased over the years, which may be due to more new antidepressant users, but also may be due to a longer duration of use. We aimed to assess the prevalence, incidence and average duration of selective serotonin reuptake inhibitor (SSRI) and tricyclic antidepressant (TCA) use in the Netherlands during 1992–2001. In addition, we assessed the incidence of long-term use of SSRIs and identified possible determinants of long-term use.
Methods: We assessed prevalence (number of current users of an antidepressant per 1000 persons assessed on a single day) and incidence (number of new users per 1000 persons per year) of antidepressant use for each year in the PHARMO record linkage system. Long-term use was defined as the consecutive use of any antidepressant for at least 12 months. Relative risks and hazard ratios were calculated and adjusted for possible determinants using Poisson and Cox regression analyses.
Results: Both prevalent and incident use of SSRIs increased during 1992–2001, while TCA use remained stable. A total of 9857 patients using SSRIs were included in a follow-up study. During the follow-up period, more patients became long-term users, either directly after the start of the initial SSRI or anytime during follow-up (29.5%). The average number of days before start of long-term use decreased from 595 days in 1991 to 19 days in 1997. Female patients, older age, previous use of benzodiazepines and being treated by a psychiatrist increased the probability of becoming a long-term user.
Conclusion: Both prevalent and incident use of SSRIs increased during the 1990s, implicating an increased number of patients starting SSRIs, but also a longer duration of use of antidepressant therapy. Over the entire follow-up period, almost 30% of the patients became long-term users at anytime during the follow-up period.

Keywords Long-term use · Antidepressants · SSRI

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Introduction

The use of antidepressants and, especially, selective serotonin reuptake inhibitors (SSRIs) has increased dramatically over the last decade [1]. An important but often neglected question is whether the increase is due to more people starting treatment or because patients who start therapy continue treatment for longer periods of time. Both features may lead to the observed rise in antidepressant use.

Depressive disorder is increasingly being recognised as a chronic and recurring illness with a strong negative and long-lasting impact on functioning and well-being equal to or even exceeding that of chronic somatic diseases. For the treatment of the acute phase, current guidelines recommend a treatment period of 4–6 weeks up to a maximum of 10 weeks. For the prevention of relapses, a further continuation of treatment varying from 4 months to 12 months is recommended and, finally, for the prevention of recurrence, maintenance treatment is advised [2, 3, 4]. However, the duration of the maintenance phase and the selection of patients for it remain under debate.

In order to separate the increasing numbers of patients starting with antidepressants from those with longer duration of use, we calculated prevalence and incidence as well as duration of antidepressant use in The Netherlands during 1992–2001. In addition, we assessed the extent of long-term use in patients who started treatment with an SSRI during 1991–1997 and identified characteristics of long-term users.

Materials and methods

Setting

Data were collected from the PHARMO database, covering medication histories of a growing population in The Netherlands. Medication histories included all information on drugs prescribed, e.g. drug type, amount and dosage, age and gender of the patient, prescriber, date of dispensing and legend duration calculated from the amount and the prescribed dosage. This database has been described in detail elsewhere [5]. All drugs were coded according to the Anatomical Therapeutic Chemical classification system [6].

Study population

The incidence, prevalence and duration of use were calculated with data covering all prescription medication histories of a population of 850,000 patients in The Netherlands from 1 January 1990 to 31 December 2001. The assessment of long-term use was performed in year-cohorts (1991–1997) of new users of SSRIs in each year during follow-up. All new SSRI users between the ages of 18 years and 85 years were included in the cohorts. New use of an SSRI was defined as a first prescription of a specific SSRI (fluoxetine, fluvoxamine, paroxetine or sertraline) and no previous use of any (other) antidepressant during the study period. All patients with less than a 1-year medication history prior to the inclusion date or less than a 1-year follow-up were excluded. To concentrate on long-term use in patients with intended antidepressive therapy, we excluded from the total ($n = 11{,}749$) all patients with only one prescription of an antidepressant during the study period ($n = 1892$). Patients were followed up until their last visit to the pharmacy or until the end of data collection.

Outcome definitions

Prevalence of antidepressant use was calculated as the number of current users of an antidepressant per 1000 persons assessed on a single random day for each year during the study period. Incidence was defined as the number of new users of an antidepressant per 1000 persons per year. New users had to have at least the prior year free from prescription of any antidepressant. Average duration of use per patient was calculated (total days of use per antidepressant per year divided by the number of users in that year) and expressed as number of days per year.

Long-term use was defined as a period of consecutive use of antidepressants, either SSRI or other, for at least 12 months as determined from the dates of dispensing and the estimated duration of use for each prescription for each individual patient. Between the end of the estimated duration and the filling of the next prescription, we allowed for a maximum lapse of 30 days, accounting for partial non-compliance. We identified the users that became long-term users directly following their initial use of an SSRI (initial long-term users) as well as at anytime during the follow-up period (anytime long-term users). We then calculated the number of initial and anytime long-term users for each year cohort.

Determinants of long-term use

We calculated relative risks to compare possible determinants of initial long-term use (including age, gender, type of SSRI, year of start of SSRI, previous use of benzodiazepines and type of prescriber) and adjusted with Poisson regression analysis. In addition, hazard ratios for the same determinants of any long-term use were modelled using Cox proportional hazard survival regression analysis.

Results

Between 1992 and 2001, prevalence and incidence of SSRI use increased from 2.2 to 17.1 per 1000 persons and from 3.7 to 14.5 per 1000 person-years, respectively. The average duration of SSRI use per year increased from 119 days to 199 days. The use of TCAs remained more or less stable during the 1990s; prevalence increased from 6.2 to 6.4, incidence decreased from 7.7 to 5.8. The average duration of TCA use increased from 165 days to 202 days. In Fig. 1, data are shown indexed for 1992.

A total of 9857 patients starting SSRI therapy were included in the analysis of long-term use (Table 1). Two-thirds of the users were female, and most patients were aged 31–45 years. Of all patients who were new SSRI users, 2978 (30.2%) stopped within 8 weeks after they started with the initial SSRI, 3192 (32.4%) continued therapy for 2–6 months, 1830 (18.6%) continued for

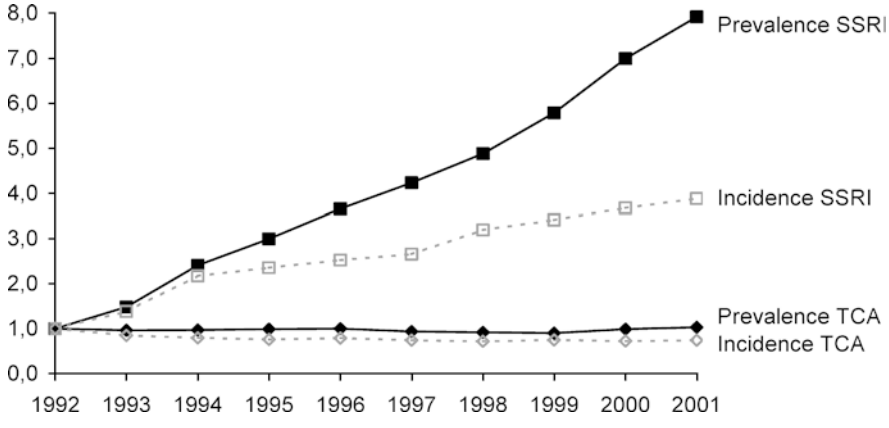

Fig. 1 Indexed prevalence and incidence per year of antidepressant use during 1992–2001 (1992 = 1)

Table 1 Possible determinants of long-term antidepressant use in new users of selective serotonin reuptake inhibitors (SSRIs), directly following initial use and any time during follow-up. *BDZ* benzodiazepines

	n	Initial long-term users *n* (%)	Relative risk* (95% confidence intervals)	Any time long-term users *n* (%)	Average time from inclusion to long-term use	Hazard ratio* (95% confidence intervals)
Total	9857	1867 (18.8)		2909 (29.5)	207	
Gender						
Female	6593	1310 (19.9)	Reference	2042 (31.0)	210	Reference
Male	3264	547 (16.8)	0.81 (0.74–0.90)	867 (26.6)	200	0.83 (0.77–0.90)
Age (years)						
18–30	1944	267 (13.7)	Reference	418 (21.5)	231	Reference
31–45	3831	785 (20.5)	1.54 (1.34–1.77)	1,226 (32.0)	217	1.54 (1.38–1.72)
46–60	2498	521 (20.9)	1.59 (1.37–1.85)	774 (31.0)	165	1.54 (1.36–1.73)
61–85	1584	284 (17.9)	1.35 (1.14–1.60)	491 (31.0)	225	1.54 (1.35–1.76)
Start year						
1991	498	62 (12.4)	Reference	159 (31.9)	595	Reference
1992	649	90 (13.9)	1.05 (0.76–1.45)	215 (33.1)	485	1.12 (0.91–1.38)
1993	1001	132 (13.2)	1.01 (0.74–1.37)	297 (29.7)	371	1.13 (0.93–1.38)
1994	1923	313 (16.3)	1.23 (0.94–1.63)	571 (29.7)	263	1.31 (1.08–1.57)
1995	1830	329 (18.0)	1.34 (1.01–1.76)	520 (28.4)	161	1.38 (1.14–1.67)
1996	1998	449 (22.5)	1.64 (1.25–2.15)	615 (30.8)	79	1.76 (1.45–2.13)
1997	1958	482 (24.6)	1.80 (1.37–2.36)	532 (27.2)	19	1.93 (1.59–2.35)
Start SSRI						
Fluoxetine	2949	403 (13.7)	Reference	741 (25.1)	295	Reference
Paroxetine	4265	924 (21.7)	1.38 (1.22–1.56)	1310 (30.7)	146	1.26 (1.15–1.39)
Fluvoxamine	2521	493 (19.6)	1.40 (1.23–1.60)	812 (32.2)	232	1.31 (1.18–1.44)
Sertraline	122	37 (30.3)	1.71 (1.21–2.41)	46 (37.7)	71	1.32 (0.98–1.79)
Prescriber						
General practitioner	7748	1387 (17.9)	Reference	2019 (26.1)	180	Reference
Psychiatrist	2073	470 (22.7)	1.29 (1.16–1.44)	890 (42.9)	266	1.68 (1.55–1.82)
History of BDZ	4942	1015 (20.5)	1.16 (1.06–1.28)	1,658 (33.5)	221	1.20 (1.11–1.29)

*Adjusted for gender, age, start SSRI, start year, prescriber and history of benzodiazepine use

7–12 months and, finally, 1867 (18.8%) continued for more than 12 months, i.e. fulfilling our definition of long-term users. These 1867 patients were identified as initial long-term users, while 2909 patients (29.5%) became long-term users at anytime during the follow-up period.

Long-term users were more often female, at least 31 years of age, more often treated by a psychiatrist than by a general physician and more often had a history of use of benzodiazepines (Table 1). Finally, a strong time-trend was seen, with patients that were included in the later cohorts more often becoming long-term users.

In order to further investigate the time to long-term use and to adjust for differences in follow-up time, we performed a Cox regression survival analysis, including the same variables (Table 1). We found an increasing rate of long-term use with later starting years, with a twofold increased chance of becoming a long-term antidepressant user in 1997 compared with 1991 [adjusted hazard ratio 1.93 (95% confidence interval 1.59–2.35)]. The average time to long-term use decreased from 595 days in 1991 to 19 days in 1997.

Discussion

The increase in overall antidepressant use in the 1990s can be largely attributed to the increase in SSRI use. This increase is explained by both more people starting with SSRIs and longer average duration of therapy. The latter finding was also seen to some extent for TCAs. Evaluation of all new SSRI users showed that one-third ended up as long-term users during an 8-year follow-up period. Almost 20% of all new SSRI users became long-term users directly following their initial start and almost one-third at any time during follow-up. New SSRI users in the late 1990s had a higher probability of becoming a long-term user compared with patients who started with a SSRI in the earlier 1990s. Treatment by a psychiatrist and a history of benzodiazepine use were also associated with long-term use.

As has been reported before, the use of antidepressants, and especially SSRIs, has increased dramatically over time [1, 7, 8, 9]. However, in these studies, no differentiation was made between increasing numbers of patients starting SSRI therapy and a continuation of initial treatment over time. An increase of prescriptions may be due to earlier detection of depressive disorder by general practitioners (GPs), broader range of indications for which SSRIs are prescribed and the effectiveness of SSRI therapy with a favourable side-effect profile [10, 11, 12, 13]. Continuation of initial therapy may be a reflection of (international) guidelines, suggesting continuation of treatment after the acute response, ranging from 4 months to 9 months, followed by a maintenance treatment for 2–5 years [3, 4, 13].

A limited number of observational studies on the duration of maintenance therapy have been reported.

Frank and Kupfer and colleagues have suggested a continuation of therapy for at least 2 years, while they showed in a double-blind placebo-controlled study that in patients with recurrent major depression and a good response to imipramine during both acute treatment and 2-year follow-up, a further continuation of treatment for 3 years reduced the risk of recurrence [14, 15, 16]. Another 5-year follow-up study, with a naturalistic design, showed that patients who had experienced more prior episodes benefited more from therapy lasting at least 8 months than patients who experienced fewer previous periods [17]. The increase in long-term use of antidepressants can be considered a reflection of better prescribing according to current guidelines on the treatment of depressive disorders. Use of antidepressants for other diagnoses (anxiety disorders, eating disorders) may have affected our findings. However, long-term treatment is also advocated for these indications [18, 19]. The higher rates of long-term use in patients treated by a psychiatrist suggest that clinical practice guidelines are more adequately followed by psychiatrists compared with GPs. However, it may indicate that psychiatrists treat more patients with severe and/or more chronic depression. The latter may also explain the higher rates of long-term use in patients with a history of benzodiazepine use. The use of benzodiazepines is common in patients with depression [20], both prior to treatment with SSRIs and concurrently [21]. Patients on benzodiazepines may have a long history of (subdiagnostical) depression and, therefore, may be more prone to long-term use of antidepressants.

Long-term use of antidepressants may not be positive in all patients. In an overview, Medawar warned not to underestimate the risks of dependence on SSRIs, as was also recognised with long-term use of benzodiazepines [22]. However, the benefits of long-term treatment have been described in a number of studies, reporting that the risk of relapse and recurrence is reduced in patients who continue treatment with antidepressants compared with those who discontinue within 6 months [23, 24, 25].

Our study may be influenced by the cohort effects of treatment in the early 1990s versus the late 1990s. Our inclusion criteria of an antidepressant-free period of at least 1 year before inclusion may have lead to a bias of selecting more ''real'' new starters and fewer restarters (after a lapse of at least 1 year) in the later part of the follow-up period. However, patients included in the beginning of the follow-up period may have had a greater chance of becoming anytime long-term users, due to the longer period of observation. Accepting these cohort effects as a limitation of this type of study, we adjusted for time in the analysis.

In conclusion, in patients starting SSRIs, we found an increasing number of long-term users in the population over time. Over the entire follow-up period, almost 30% of the patients became long-term users at any time during the follow-up period. Female patients, older age, previous use of benzodiazepines and being treated by a psychiatrist increased the probability of becoming a long-term user.

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