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Factors associated with switching and combination use of antidepressants in young Swedish adults

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SUMMARY

Aims: Little is known on factors associated with switching and combination use of antidepressants. Our aim was to describe such use and to analyse the association with socioeconomic factors and level of care in Swedish adults aged 20–34 years. **Methods:** Individuals, aged 20–34 years, who purchased an antidepressant in January–June 2006, and who had not purchased any antidepressant in the preceding 6 months (n = 24,897) were followed from 6 up to 12 months. Among those who purchased ≥ 2 antidepressant substances, switchers were defined as those who did not fulfil the requirements for combination use. Data on purchased antidepressants and socioeconomic characteristics were obtained from the Swedish Prescribed Drug Register and Statistics Sweden. The association between (i) ≥ 2 antidepressants or (ii) switching, respectively, and socioeconomic factors as well as level of care was analysed with multiple logistic regression. **Results:** A total of 4254 individuals (17%) purchased ≥ 2 antidepressant substances, and the remaining 20,643 (83%) purchased one antidepressant. The adjusted odds ratio (OR) for purchase of ≥ 2 antidepressants (vs. purchase of one antidepressant only) was higher among those who started on mirtazapine compared with selective serotonin re-uptake inhibitors: 2.23 (95% confidence interval: 1.93–2.57), and lower in individuals with high education: 0.64 (0.54–0.75), and shorter length of follow-up: 0.73 (0.62–0.85). Among those with ≥ 2 antidepressants, 71.6% were classified as switchers. The adjusted OR for switching (vs. combination use) were higher among divorced/widows/widowers: 1.61 (1.05–2.49), and lower among individuals with short university education: 0.58 (0.43–0.78), those starting on mirtazapine: 0.78 (0.62–0.97), and when treatment was initiated in psychiatric care: 0.75 (0.63–0.88). **Conclusions:** One of six new users purchased at least two antidepressants, the majority were classified as switchers. Purchase patterns were associated with socioeconomic characteristics, in particular level of education, type of first purchased antidepressant, and level of care initiating treatment.

What's known
About one of five to ten individuals on treatment with antidepressants uses two or more antidepressant substances. Switching and combination use of antidepressants is common, especially in adults under 35. The magnitudes and the distribution between switchers and combination users differ extensively between studies. Age, type of antidepressant purchased at initiation and prescriber have been associated with prescribing patterns.

What's new
In this register-based study, one of six new antidepressant users purchased at least two antidepressant substances within 12 months from the first purchase, and the majority of these were classified as switchers. Factors which were associated with purchase patterns were socioeconomic characteristics, especially level of education, type of antidepressant at initiation and level of healthcare where antidepressant treatment was initiated.

Introduction

On a population level, most antidepressants are about equally effective in improving depressive symptoms. However, individual differences in effectiveness exist and adverse drug reaction profiles differ between antidepressant agents (1–3). Therefore, switching to another antidepressant or augmentation with another antidepressant for combination use may be necessary to achieve the desired effect. Antidepressants are often also used for other indications such as anxiety and neuropathic pain (4,5).

Among new antidepressant users, between 9% (6) and 20% (7–9) use at least two different antidepressants, a treatment strategy which is common among users younger than 35 years (10). Indeed, knowledge on treatment in this age group is important since sick-listings and disability pensions related with mental health problems, especially depression, have increased (11–13) and early discontinuation of antidepressant use is common (14). Among those using at least two antidepressants, the distribution between switching and combination use varies (9,10,15,16). Reported switching rates range from 4% up to 40% (9,10,15–23), and differ by age, by type of antidepressant used at initiation, and by prescriber (9,21,23). Combination use, on the other hand, varies between 2% and 43% (9,10,15,16).

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Previous studies have shown that register data are valuable for assessments of course of drug treatment over time. Furthermore, although treatment strategies as regards antidepressants in young adults have been evaluated to some extent, little is known as to whether such strategies are associated with socioeconomic characteristics of the patients. Furthermore, little is known regarding the specific antidepressant substance chosen for first and second line treatment. Thus, the aim of the present population-based nationwide register study was to investigate switching and combination use of antidepressants in adults aged 20–34 years, and to analyse socioeconomic factors and level of care as potential predictors for such use. Furthermore, we wanted to analyse how different procedures to differentiate between switching and combination use affect the results in Swedish register data.

Methods

Setting and study population

The study population encompassed all individuals in Sweden aged 20–34 with at least one purchased antidepressant between January 1 and June 30, 2006 recorded in the Swedish Prescribed Drug Register, SPDR. SPDR includes information on all prescribed and dispensed medicines in Sweden since July 1, 2005. To include new treatment episodes only, we excluded those who had purchased any antidepressant within 6 months before the index date. Thus, a 6-month period without any purchase was ascertained. The day of the first purchase was denoted the index date. We also excluded those who used multi-dose dispensed drugs because the registration of these differs from that of ordinary prescriptions. Furthermore, those who died or emigrated during the study period were excluded (Figure 1).

The study period started January 1, 2006 and ended December 31, 2006. Thus, each individual was followed for 6–12 consecutive months from the index date within this time window. The length of follow-up varied depending on when the index date took place. We chose to allow for different length of follow-up as we were interested in how this affected the prevalence of ≥ 2 antidepressants, as well as the distribution between switching and combination use.

Data

For included individuals, data on all purchased antidepressants [according to the anatomical therapeutic chemical (ATC) classification system (ATC-code N06A)] (24) during the study period were collected from the Swedish Prescribed Drug Register (25). The register includes information on the patient's age, gender, the dispensed pharmaceutical product (date of issue and purchase, amount dispensed, pharmaceutical product, cost), and the type of care facility where the prescription was issued. Antidepressants were categorised as (i) tri-cyclic antidepressants (TCA, ATC-code N06AA), (ii) selective serotonin re-uptake inhibitors (SSRI, N06AB), (iii) serotonin and norepinephrine re-uptake inhibitors (SNRIs, N06AX16 or N06AX21), (iv) mirtazapine (N06AX11) or (v) other antidepressants (all other substances in the ATC-group N06A). Type of care facility was categorised as primary care, psychiatric care or other specialised care including all other disciplines. Length

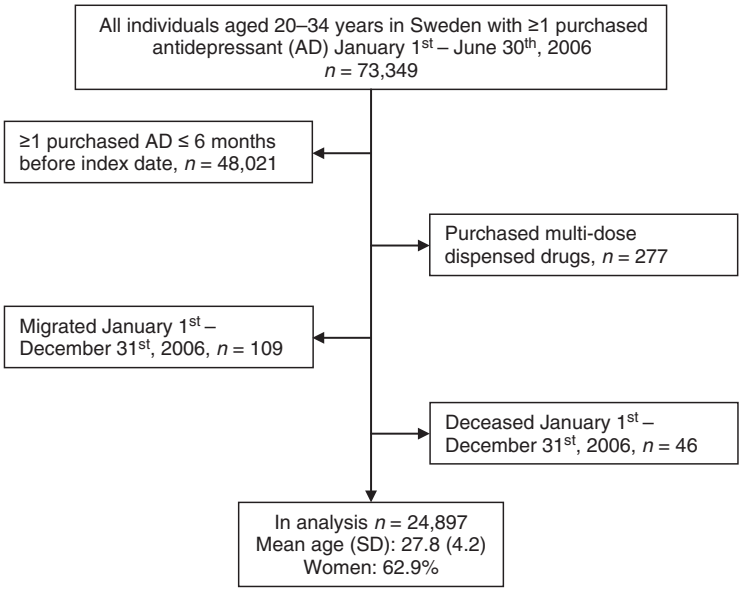

Figure 1 Flowchart of inclusion criteria applied for the study population. AD, antidepressant

of follow-up was defined as the time from the index date to the end of the study period.

Data on socioeconomic characteristics were collected by record linkage to the Longitudinal integration database for health insurance and labour market studies (LISA) and the Total Population Register at Statistics Sweden. Marital status by December 31, 2006 was categorised as either single, married (including registered partnership for same-gender couples), or divorced/widow/widower. The individuals' and their parents' country of birth were combined into a variable denoted 'migration background' which reflected the national origin: born in Sweden, two parents born in Sweden; born in Sweden, one parent born outside Sweden; born in Sweden, both parents born outside Sweden; born outside Sweden, at least one parent born in Sweden and born outside Sweden, two parents born outside Sweden. As regards social assistance, the individuals were categorised as either recipients or not. Recipients were defined as those receiving a cash benefit in the absence of other income in 2005, either themselves or any other household member. Highest level of education was defined at the end of the 2006 spring term. Occupation type was recorded in November 2005 and categorised as upper white-collar, lower white-collar, blue-collar and others which included armed forces, farmers, market gardeners, forestry and related workers. Whether or not the individual had an annual income corresponding to less than 60% of the median income in 2005 was used as an indicator of low income level. Date of death and migration data was collected at the end of 2006.

Ethical approval was obtained from the regional ethical review board in Gothenburg and was a prerequisite for data collection.

Outcome measures

For each individual, the number of antidepressant substances purchased during the study period was assessed. Individuals who purchased ≥ 2 antidepressants during the study period were classified as either combination users or switchers. A combination user was defined as an individual who, at any time during the study period, either (i) purchased ≥ 2 antidepressant substances on the same day or (ii) purchased a specific antidepressant substance at least once more within 125 days of having purchased another antidepressant. Individuals who purchased ≥ 2 antidepressant substances but did not fulfil the combination user criteria were classified as switchers. For example, an individual who purchased citalopram on February 12, April 17 and June 18, and venlafaxine on May 10, would be classified as a combination user. Accordingly, an individual who purchased citalopram on February 12, April 17, and venlafaxine on May 10 and July 15 would be defined as a switcher. The choice of 125 days was based on the Swedish Pharmaceutical Benefit Scheme, which reimburse a maximum of 90 days' drug supply at one purchase occasion (26). In practice, packages for 100 days are often dispensed because of package sizes of 98 or 100 units. Thus, allowing for at least 80% adherence, one filled prescription would last for a maximum of 125 days.

For those who purchased two and three antidepressant substances during the study period, the subsequent order and the number of days between purchases of different antidepressant substances were assessed.

Two sensitivity analyses were performed. First, we assessed the influence on the distribution between combination users and switchers when number of days was altered from 125 to 100 and 150 days. Second, the influence of excluding dispensed start packages of 32 tablets or less was investigated.

Statistical analysis

Pearson's χ^2-test was used to compare categorical variables and Student's *t*-test was used for comparisons of means. Multiple logistic regression was performed to analyse if purchase of ≥ 2 antidepressants or switching, respectively, was associated with gender, type of first purchased antidepressant, length of follow-up, education level, marital status, occupation type, migration background, income level, receiving social assistance and type of healthcare facility where the first antidepressant prescription was issued. This was done in a two-step process. First, univariate analyses were conducted followed by a multiple regression analysis including gender and type of first purchased antidepressant and variables with a $p < 0.10$ in the univariate analyses. Crude and adjusted odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. Income level was not included in the final models since $p > 0.10$ in the univariate analyses. Length of follow-up was not included in the final models for switching since $p > 0.10$ in the univariate analyses. Data management and statistical analyses were performed with SAS version 9.1.

Results

Participants and characteristics

In total, 24,897 individuals aged 20–34 years (62.9% women) were included in the study (Figure 1). This corresponds to 1.5% of the population aged 20–34 years in Sweden on December 31, 2006 (n = 1,691,356) (27).

First purchased antidepressant

A total of 20,643 (82.9%) individuals purchased one antidepressant substance only during the study period (Table 1). An SSRI was purchased as first antidepressant by 19,017 (76.4%) individuals (Table 2). The three most frequently first purchased antidepressant substances were citalopram, sertraline and fluoxetine.

Use of at least two antidepressant substances

A total of 4254 (17.1%) individuals purchased ≥ 2 antidepressant substances during the study period (Table 1). As shown in the right hand section of Table 2, the proportion of individuals who purchased ≥ 2 antidepressant substances varied by first purchased antidepressant, ranging from 14.0% for amitriptyline to 29.7% for mianserine. To purchase ≥ 2 antidepressants was more common for those who first purchased mirtazapine or an antidepressant in the group other antidepressants, compared with those who first purchased an SSRI (Table 3). The odds were lower among those who started late during the run-in period when compared with early in the period, among those with an educational level above mandatory school, and when the index prescription was issued in a facility other than primary care and psychiatric care (Table 3).

Combination use and switching

Among those who purchased ≥ 2 antidepressants, 1209 (28.4%) individuals were classified as combination users, corresponding to 4.9% of the total study population. Among combination users who purchased two antidepressant substances, 825 (14.6%) individuals, purchased both antidepressants on the same day. Among combination users with two antidepressants, the mean number of days ± standard deviation (SD) between the first and the second purchase of an antidepressant was 88.4 ± 79.5.

Of those with ≥ 2 antidepressants, 3045 (71.6%) individuals were defined as switchers. This corresponds to 12.2% of the total study population. For switchers who purchased two antidepressant substances, the mean number of days ± SD between the purchase of first and second antidepressant was 126.0 ± 87.9 days.

There was no difference in the proportion who purchased a start package at index date between those defined as switchers compared with those defined as combination users (40.2% vs. 38.2%, p = 0.23).

The odds for switching were higher among divorced/widows/widowers compared with singles (Table 4). The odds were lower among those who first purchased mirtazapine, compared with those who first purchased an SSRI, among those with a higher/university education shorter than 2 years, and among those whose index prescription was issued in a general psychiatric care facility (Table 4).

Table 5A, B show first and subsequently purchased antidepressant for switchers and combination users, respectively, among those who purchased two and three antidepressant substances. Among switchers, switching from one SSRI to another was most common, followed by switching from an SSRI to an SNRI or mirtazapine (Table 5A). Among combination users, concurrent use of an SSRI and mirtazapine was

Table 1 Number of antidepressant substances purchased per individual during the study period (January 1–December 31 2006) (n = 24,897)

Number of antidepressant substances	n (%)
1 antidepressant	20,643 (82.9)
2 antidepressants	3454 (13.9)
3 antidepressants	667 (2.7)
4 antidepressants	117 (0.5)
≥ 5 antidepressants	16 (0.06)

Table 2 Number of individuals (percentage of total) who first purchased each antidepressant substance (left hand side of the table) and who used ≥ 2 antidepressant substances (percentage of individuals on each substance, right hand side of the table) (n = 24,897). Substances purchased by < 20 individuals were not included in the table

First purchased antidepressant	Number of individuals (% of study population) n (%)	Number of individuals who purchased at least two antidepressant substances (% among individuals who purchased the antidepressant as first antidepressant) n (%)
TCA	1794 (7.2)	285 (15.9)
Amitryptiline	1451 (5.8)	203 (14.0)
Clomipramine	272 (1.1)	57 (21.0)
Nortryptiline	14 (0.1)	5 (35.7)
Trimipramine	51 (0.2)	20 (39.2)
SSRI	19,017 (76.4)	2970 (15.6)
Citalopram	7707 (31.0)	1261 (16.4)
Escitalopram	1658 (6.7)	318 (19.8)
Fluoxetine	2254 (9.1)	360 (16.6)
Paroxetine	1248 (5.0)	171 (13.7)
Sertraline	6144 (24.7)	859 (14.0)
SNRI	1713 (6.9)	334 (19.5)
Venlafaxine	1168 (4.7)	202 (17.3)
Duloxetine	545 (2.2)	132 (24.2)
Mirtazapine		
Mirtazapine	2036 (8.2)	569 (27.9)
Other antidepressants	2373 (9.5)	665 (28.0)
Reboxetine	86 (0.4)	26 (30.2)
Mianserine	192 (0.8)	57 (29.7)
Moclobemide	48 (0.2)	10 (20.8)

Table 3 Multiple logistic regression analysis of possible predictors for purchase of ≥ 2 different antidepressants substances compared with one antidepressant (n = 24,897)

	Crude OR (95% CI)	Adjusted OR (95% CI)
Women	0.98 (0.92–1.05)	1.16 (1.05–1.28)
Type of first purchased antidepressant		
SSRI	1.00	1.00
TCA	1.02 (0.89–1.17)	1.03 (0.85–1.22)
SNRI	1.31 (1.15–1.48)	1.18 (1.00–1.39)
Mirtazapine	2.10 (1.89–2.36)	2.23 (1.93–2.57)
Other antidepressants	2.15 (1.69–2.74)	2.18 (1.56–3.05)
Month of index date		
January	1.00	1.00
February	0.93 (0.83–1.03)	0.98 (0.86–1.14)
March	0.86 (0.77–0.95)	0.92 (0.80–1.06)
April	0.84 (0.75–0.94)	0.83 (0.71–0.96)
May	0.71 (0.64–0.80)	0.75 (0.64–0.87)
June	0.66 (0.59–0.75)	0.73 (0.62–0.85)
Migration background		
Born in Sweden, two parents born in Sweden	1.00	1.00
Born in Sweden, one parent born outside Sweden	1.20 (1.07–1.34)	1.25 (1.09–1.45)
Born in Sweden, both parents born outside Sweden	1.11 (0.95–1.30)	1.08 (0.89–1.33)
Born outside Sweden, one or both parents born in Sweden	1.42 (0.84–2.39)	1.86 (0.99–3.51)
Born outside Sweden, both parents born outside Sweden	1.10 (0.94–1.30)	0.93 (0.74–1.17)
Social assistance (Yes vs. no)	1.41 (1.30–1.53)	1.19 (1.03–1.37)
Education		
Mandatory education (0–10 years)	1.00	1.00
Upper secondary school	0.81 (0.75–0.88)	0.78 (0.69–0.89)
Higher education < 2 years	0.76 (0.66–0.87)	0.72 (0.59–0.88)
Higher education ≥ 2 years	0.60 (0.54–0.67)	0.64 (0.54–0.75)
Marital status		
Unmarried	1.00	1.00
Married	1.03 (0.94–1.12)	1.07 (0.95–1.21)
Divorced or widow/widower	1.33 (1.15–1.53)	1.14 (0.91–1.42)
Occupation		
Upper white collar	1.00	1.00
Lower white collar	1.35 (1.21–1.51)	1.12 (0.97–1.28)
Blue collar	1.50 (1.34–1.67)	1.25 (1.09–1.44)
Other	0.85 (0.53–1.37)	0.64 (0.37–1.12)
Prescribing facility		
Primary care	1.00	1.00
Psychiatric care	1.28 (1.19–1.38)	1.16 (1.05–1.28)
Other specialised care	0.72 (0.63–0.83)	0.74 (0.63–0.87)

Results are presented as crude and adjusted odds ratios (OR) with 95% confidence intervals (95% CI).

most common followed by concurrent use of SSRI and other antidepressants (Table 5B).

When assessing both combination use and switching together for those with two and three antidepressant substances, the most common choice when an additional antidepressant was initiated was to switch from one SSRI to another (24.5%, n = 1008), followed by switch from an SSRI to an SNRI (12.4%, n = 511) or mirtazapine (9.9%, n = 410).

Sensitivity analyses

For individuals who purchased ≥ 2 antidepressants, the distribution between combination users and switchers was marginally affected by changing the number of days allowed between consecutive purchases of different antidepressant substances (from 125 to 100 and 150 days, respectively) (Table 6). Excluding those who first purchased a start package did not affect the switching rates (72.7% vs. 71.0%, p = 0.23).

Table 4 Multiple logistic regression analysis of possible predictors for switching (compared with combination use) among those with ≥ 2 antidepressants (n = 4254)

	Crude OR (95% CI)	Adjusted OR (95% CI)
Women	1.14 (0.99–1.31)	1.12 (0.95–1.32)
Type of first purchased antidepressant		
SSRI	1.00	1.00
TCA	0.96 (0.73–1.26)	0.90 (0.64–1.26)
SNRI	0.99 (0.77–1.27)	0.98 (0.73–1.32)
Mirtazapine	0.78 (0.65–0.95)	0.78 (0.62–0.97)
Other antidepressants	0.88 (0.57–1.37)	1.04 (0.62–1.78)
Migration background		
Born in Sweden, two parents born in Sweden	1.00	1.00
Born in Sweden, one parent born outside Sweden	1.09 (0.87–1.36)	1.07 (0.84–1.35)
Born in Sweden, both parents born outside Sweden	1.24 (0.90–1.71)	1.25 (0.88–1.78)
Born outside Sweden, one or both parents born in Sweden	2.11 (0.61–7.30)	2.26 (0.65–7.94)
Born outside Sweden, both parents born outside Sweden	1.50 (1.05–2.13)	1.40 (0.97–2.05)
Education		
Mandatory education (0–10 years)	1.00	1.00
Upper secondary school	1.00 (0.84–1.18)	0.94 (0.77–1.15)
Higher education < 2 years	0.66 (0.50–0.86)	0.58 (0.43–0.78)
Higher education ≥ 2 years	0.84 (0.68–1.04)	0.85 (0.66–1.08)
Marital status		
Unmarried	1.00	1.00
Married	1.09 (0.91–1.31)	0.92 (0.74–1.15)
Divorced or widow/widower	1.41 (1.04–1.91)	1.61 (1.05–2.49)
Prescribing facility		
Primary care	1.00	1.00
Psychiatric care	0.73 (0.63–0.84)	0.75 (0.63–0.88)
Other specialised care	1.04 (0.77–1.41)	1.02 (0.74–1.42)

Results are presented as crude and adjusted odds ratios (OR) with 95% confidence intervals (95% CI).

Table 5 First and subsequently purchased antidepressant among those who purchased two or three antidepressant substances for individuals defined as switchers (A, n = 3045) and combination users (B, n = 1209), respectively

First purchased antidepressant	TCA	SSRI	SNRI	Mirtazapine	Other antidepressants*
(A) Switching					
TCA	8 (0.3)	119 (4.0)	33 (1.1)	29 (1.0)	9 (0.3)
SSRI	100 (3.3)	1008 (33.7)	511 (17.1)	410 (13.7)	84 (2.8)
SNRI	21 (0.7)	132 (4.4)	31 (1.0)	41 (1.4)	9 (0.3)
Mirtazapine	20 (0.7)	270 (9.0)	80 (2.7)	0 (0.0)	10 (0.3)
Other antidepressants*	6 (0.2)	34 (1.1)	16 (0.5)	6 (0.2)	4 (0.1)
(B) Combination use					
TCA	5 (0.4)	44 (3.9)	6 (0.5)	10 (0.9)	5 (0.4)
SSRI	47 (4.2)	89 (7.9)	81 (7.2)	373 (33.0)	177 (15.7)
SNRI	7 (0.6)	30 (2.7)	5 (0.4)	36 (3.2)	8 (0.7)
Mirtazapine	3 (0.3)	123 (10.9)	44 (3.9)	0 (0.0)	8 (0.7)
Other antidepressants*	0 (0.0)	20 (1.8)	7 (0.6)	2 (0.2)	0 (0.0)

Values are presented as n (% of switchers and combination users). *Moclobemide, tryptophan, mianserine, nefazodone or reboxetine.

Discussion

In this nationwide population-based study, we found that one of six Swedish adults aged 20–34 years who initiated antidepressant treatment purchased either two or more antidepressants from start, or switched to or combined with another antidepressant substance later on. The majority of those who purchased

Table 6 Number of switchers among individuals who purchased ≥ 2 antidepressants during the study period (n = 4254) when number of days allowed between purchases was changed from 125 days to 100 and 150 days, respectively, by number of purchased antidepressants

	100 days n (%)	125 days n (%)	150 days n (%)
At least two antidepressants	3111 (73.1)	**3045 (71.6)**	2991 (70.3)
Two antidepressant substances	2680 (77.6)	**2629 (76.1)**	2583 (74.8)
Three antidepressant substances	373 (55.9)	**362 (54.3)**	354 (53.1)
Four antidepressant substances	52 (44.4)	**50 (42.7)**	50 (42.7)
At least five antidepressant substances	6 (37.5)	**4 (25.0)**	4 (25.0)

Values are presented as number of switchers (% switchers in each group).

two or more antidepressants switched from one to another, most often from an SSRI to another. Socioeconomic characteristics of the patient, in particular education, type of antidepressant at initiation and level of care, were associated with purchase of at least two antidepressants and switching. The time window applied to distinguish between combination use and switching was found to be robust.

The finding that one of six adults purchased at least two antidepressants during the study period is somewhat higher compared with some studies (6–8) but lower than others (7,9). Use of at least two antidepressant substances was associated with choice of antidepressant at initiation, which is in accordance with previous findings (10). In addition, McCombs et al. reported that race and urban/rural residence were factors that influenced use of at least two antidepressants (10). The current data did not allow us to analyse whether these factors were important in the Swedish setting. Migration background influenced to some extent, although not as strongly as for early discontinuation (14).

In the present study, more than one of eight new antidepressant users switched to another antidepressant. Previous studies have reported a wide range of switching rates, from rates below or comparable to our results (9,15,17,18,20–23) to considerably higher rates (16,19). It is likely that the length of follow-up affects the results; as can be expected we found that the proportion of antidepressant users who purchased at least two antidepressants increased with longer follow-up. Some of the previous studies had a longer follow-up period (9,18,21) which might have affected the estimates. The length of antidepressant free run-in period can also influence the results and this varied from 6 (19,20,23), and 12 months (9,18,21), up to 2 years (17). Another explanation for the differences in the reported figures is that some studies calculate switching among all who initiated treatment (19), whereas others include only those who purchased at least two antidepressants. Moreover, other reasons for disparities are the use of data on prescribed or purchased medicines (23), requirements that the second antidepressant should be bought within a certain time frame of the first antidepressant (9,19) or the index date (20), restricting study population to those with a depression diagnosis (9,15,19,21), excluding certain comorbidities (9) and analysing only a limited number of antidepressants (15,19–21). Furthermore, we found that switching was more common when the prescription had been issued in psychiatric care which is in line with previous studies (9,21).

Combination use was less common than switching in the present study which is in accordance with a previous study (16), although others reported higher rates of combination use (9,10). The reason for disparities in the prevalence of combination use can be that different definitions of this prescribing pattern can be applied, much because of different healthcare systems. In our study, switching and combination use was more common among those who purchased mirtazapine or an uncommon antidepressant as compared with an SSRI. These findings on mirtazapine may not be surprising since this substance differ from other antidepressants regarding pharmacodynamics properties. Therefore, it may also be used as a soporific. Two studies reported that treatment changes were equally common among those who initiated with an SSRI and an SNRI but higher among those who initiated with a TCA (9,23). To the best of our knowledge, these studies are the only ones that have previously assessed the longitudinal course of antidepressant treatment when it comes to consecutive choice of substances. Interestingly, our results are in line with theirs; an SSRI was the most common second line choice of antidepressant irrespective of type of antidepressant chosen as first line treatment (23).

As far as we are aware, our study is the first one to assess the influence of both socioeconomic

characteristics and prescribing factors on the likelihood for antidepressant switching and combination use. Previous studies have included more scarce information on socioeconomic characteristics. Beside gender and age, information on health plans (9,10,16,21) and race (10) have been included as covariates, whereas our analyses also contribute with information on work position, income, educational level, marital status and migration background. The reasons for these differences are unclear. Differences in health literacy between different groups of the population might contribute to differences in how medicines are used.

At least 6 months was considered a sufficient length of follow-up to provide a reasonable chance of receiving more than one antidepressant for a new user. To investigate how the length of the follow-up period affected the rate of individuals who purchased at least two antidepressants, we allowed varying length of follow-up and accounted for this in the analyses. As expected, there was a clear downward gradient in use of at least two antidepressants with shorter follow-up. This was not found when comparing switching and combination use among those with at least two antidepressants, which could be an indicator that this definition was not sensitive to length of follow-up.

Strengths and limitations

An important strength of the present study is that all individuals in the studied age group were included in the analyses, resulting in almost 25,000 individuals. Furthermore, the unique personal identity number, which makes record-linkage possible, was an important prerequisite to evaluate the research question of the present study. Another strength is that we have evaluated a pharmacoepidemiological approach to analyse register data as regards treatment course over time; to investigate how the length of the follow-up period affected the rate of individuals purchasing at least two antidepressants, we allowed varying length of follow-up and accounted for this in the analyses. Furthermore, the finding that the results for switchers/combination users did not vary according to length of follow-up may indicate that our definition was robust. In addition, the fact that the results were not affected by altering the interval length and excluding start packages further supports our definition of switching/combination use.

A limitation of the present study is the length of follow-up. Indeed, available data can only guarantee that no antidepressant prescriptions were filled during the 6 months preceding the index date since the Swedish Prescribed Drug Register was newly established when data collection was done (25). Therefore, the study population may encompass a mix of naïve users and those with earlier treatment episodes of antidepressants. Furthermore, our results do not distinguish between first and second line use for those who purchased at least two antidepressants on the same day; the first antidepressant is the one with the ATC-code that occurs first in alphabetical order. However, this was rather uncommon and is not likely to affect the results. Another limitation of this study is that we do not have any information regarding the indication for use or the severity of the disease; antidepressants can be used to treat several diseases and conditions. Thus, the present study does not allow any conclusions regarding reasons for switching and augmentation which may include limited efficacy or occurrence of adverse reactions. Nor did we have any information on other medications prescribed or whether the purchased medicines were consumed by the patient or not, purchase is a proxy for use in this study. Furthermore, in the Swedish Prescribed Drug Register, dosages are only given as free text and thus we could not assess whether adequate doses were prescribed.

Conclusions

In this population-based nationwide study, use of at least two antidepressants was associated with type of first purchased antidepressant, length of follow-up, socioeconomic characteristics, as well as type of health-care facility initiating treatment. The majority of those using at least two antidepressants were switchers. The odds for switching as compared with combination use were higher among divorced/widows/widowers and less common among those who started with mirtazapine, among those with a higher education shorter than 2 years and when treatment was initiated within psychiatric care. Together, the findings suggest that quite many patients need a second-line treatment when it comes to antidepressants, either a switch or an augmentation. Moreover, the results suggest that several factors may predict the use of more than one antidepressant and switching in different ways. Hence, the mechanisms might differ and it is therefore important to avoid lumping all treatment changes together but instead distinguish between switching and combination use.

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Author contributions

All authors designed the study together, MP and KAS did the data analyses and SW took part in interpretation of analyses. KAS and SW wrote the draft and all authors actively contributed in revising the manuscript. KAS received a post doc grant from the Swedish Lundbeck foundation which funded the data collection.

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