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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Changes in the prescribing pattern of antidepressant drugs in elderly patients: an Italian, nationwide, population-based study

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Abstract
Background Despite the high use of antidepressants (ADs) among the elderly, there is limited information about the prescribing pattern of these drugs in the Italian elderly population. The aim of this study was to analyze the trend in the use of ADs in the Italian elderly patients in the years 2003-2009, and specifically, to evaluate rates and predictors of AD treatment discontinuation in depressed older patients.
Methods The nationwide general practice Health Search Database (HSD) was used to identify AD users aged 65 years old and over from 2003 to 2009. ADs were categorized as (1) selective serotonin reuptake inhibitors (SSRIs); (2) serotonin-norepinephrine reuptake inhibitors (SNRIs); (3) tricyclic antidepressants (TCAs); (4) noradrenergic and specific serotonergic antidepressants (NaSSAs); and (5) other ADs. Incidence and prevalence of AD use per 1,000 inhabitants was calculated by drug class and single compound. We also measured rates and predictors of AD discontinuation (i.e., treatment gap≥60 days) during the first year of therapy.
Results Overall, 39,557 AD users ≥65 years (17 % of the total HSD elderly population) were included in the study. SSRIs were increasingly and most frequently prescribed ADs (102.7-195.3 per 1,000 over seven years). The most common indications for AD use were depression and anxiety. Overall, 14 % of AD users continued their AD medication without treatment gaps, 27 % were intermittent AD users and 58 % discontinued their ADs during the first year of follow-up. Specific AD classes such as TCAs and 'other ADs were found to be predictors of discontinuation. In depressed patients, the use of NaSSas, TCAs and 'other ADs as well the concomitant use of >5 drugs (other than ADs) and living in Southern Italy were more likely to predict discontinuation.
Conclusion ADs, especially SSRIs, are widely and increasingly prescribed in elderly Italian patients in recent years. The observed high AD discontinuation rates are likely to impact the achievement of a therapeutic endpoint in depressed patients. Patients who are at high risk of AD discontinuation such as those receiving multi-drug therapy or living in Southern Italy should be monitored more closely to improve benefits of AD treatments.

Keywords Antidepressive agents · Aged · Primary health care · Italy · Pharmacoepidemiology

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Introduction

Late-life depressive disorder is a common and potentially debilitating psychiatric disorder which constitutes an important public health concern [1]. A cross-sectional study in 11 European countries found that Italy has the highest prevalence of late-life depressive disorder at 29.7 %, second only to France. The management of late-life depressive disorder in Italy is, therefore, a matter of particular clinical relevance [2].

AD use has increased steadily in the past 15–20 years, particularly since the introduction of the selective serotonin reuptake inhibitors (SSRIs) and newer antidepressants such as venlafaxine [3, 4], and also as a result of broadening indications for AD use, which in Italy currently include diabetic peripheral neuropathic pain, nervous bulimia, migraine prophylaxis and anxiety disorders such as social anxiety disorder, generalised anxiety disorder, post-traumatic stress disorder, obsessive compulsive disorder and panic disorder. Nevertheless, underutilisation of ADs among older depressed patients is also a concern [5]. The need to investigate the use of ADs in elderly patients is emphasised by the frequent occurrence of polypharmacy and age-related pharmacokinetic changes in older adults, all of which increase the risk of adverse drug reactions.

Recently, a number of nationwide studies investigated the prescribing patterns of AD use in the Italian primary care setting. However, none of these studies explored the characteristics of AD use in detail, particularly regarding patterns of discontinuation in older patients [6-10, 11]. It is critical to address this research gap as AD discontinuation rates are reportedly as high as 70 % or more within six months from the beginning of AD therapy in depressed patients [4]. Such early AD discontinuation increases the risk of relapsing depressive symptoms [12]. For this reason, National Institute for Health & Clinical Excellence (NICE) guidelines advise a minimum of six month treatment [13] while the World Health Organisation (WHO) advises at least 9-12 month treatment for depression [14].

With these considerations in mind, our aims were: a) to analyse the trend in the use of ADs in an Italian elderly population during the years 2003-2009 in an outpatient setting; b) to characterise users of different classes of ADs; and c) to assess rates and predictors of AD treatment discontinuation in elderly depressed patients in the same setting.

Methods

Data source

As a data source, we used the nationwide Italian general practice "Health Search" database (HSD). Data in HSD is derived from a network of approximately 900 general practitioners (GPs) from all over Italy who voluntarily electronically register clinical patient data from their routine clinical practice and attend training programmes related to data entry [15]. We selected 650 GPs whose data entries fulfilled quality criteria, covering a population of 1,166,076 patients. The database contains anonymised clinical data (diagnoses, patient referrals and clinical investigations' results) and prescription data (drug name, prescription date, number of days' supply given) for all the medications which are reimbursed by the National Health System (NHS) [15]. Data within the HSD is coded using internationally recognised codes such as the Anatomical Therapeutic Chemical (ATC) classification system for drugs and the 9th version of the International Classification of Disease, Clinical Modification (ICD-9 CM) for medical diagnoses. The research validity of the HSD data for conducting pharmacoepidemiological research has been confirmed elsewhere [16-18].

Study population

Patients who were 65 years or older and alive during the observation period, with at least one year of clinical data prior to study entry, and who received at least one AD prescription between 1 January 2003 and 31 December 2009 were identified from HSD and included in the cohort.

Drug exposure

Antidepressant drugs were the primary exposure of interest. AD users were identified through prescription data and classified on the basis of the class of AD being used: (1) noradrenergic and specific serotonergic antidepressants/noradrenalin reuptake inhibitors (NaSSAs; mianserin (N06AX03) and mirtazapine (N06AX11) (2) selective serotonin reuptake inhibitors (SSRIs; ATC: N06AB); (3) serotonin-noradrenaline reuptake inhibitors (SNRIs): duloxetine (N06AX21) and venlafaxine (N06AX16); (4) tricyclic antidepressants (TCAs; N06AA); (5) 'other ADs,' namely non-selective monoamine oxidase inhibitors (MAOIs), monoamine oxidase A inhibitors and others (N06AF*, N06AG* and other N06AX* not previously included). The prescription duration was calculated using the number of dispensed drug units and the dosage regimen provided on the prescription. Agomelatine was introduced in the Italian market in 2010 and is not currently covered by NHS. For this reason, the use of this drug could not be evaluated in this study.

Covariates

As regards the characterization of AD users, we explored the demographics and clinical characteristics of the patients at the first AD prescription (i.e., index date), taking into account most frequent chronic diseases and possible contraindications to some antidepressants: hypertension, dyslipidemia, type II diabetes, obesity (BMI>30 kg/m^2 or based on the ICD-9 code), coronary heart disease, cerebrovascular disease, congestive heart failure, cardiac arrhythmia, peripheral vascular disease, chronic kidney disease, chronic liver disease, thyroid disorders, and cancer. In addition, the indication of AD use was retrieved and categorized as depressive disorder, anxiety disorder, depression associated with dementia, headache/

migraine, other neuro-psychiatric disorders, and 'other or not otherwise specified' (painful bone and joint disorders, cancer etc.). The Charlson Index, a proxy of clinical severity based on the measure of co-morbidity applied to clinical administrative data [19] was calculated using the above data for each patient by assigning numerical weights to disease states [20].

In addition, the concomitant use (within six months from the first prescription of AD) of the following medications was evaluated: vitamin K antagonists, heparins and enzymes (B01AA*, BO1AB*, BO1AD*), antihypertensive agents (C02*, C03*, C07* to CO9*), cardiac therapy (C01*), immunosuppressants (L04A*), systemic corticosteroids (H02*), non-steroidal anti-inflammatory drugs (NSAIDs) (M01A*) and other neuropsychiatric medications: anti-Parkinson drugs (N04*), antiepileptics (N03*), antipsychotics (N05A*), anxiolytics (N05B*), opioids (N02A*) and anticholinesterases (N06DA*). The total number of individual medications taken by the AD users at the time of the AD prescription was also calculated.

Data analysis

The annual prevalence and cumulative incidence of AD treatment was measured by class and individual AD over the study period. The annual prevalence of AD treatment was calculated as the number of AD users (i.e., at least one prescription in the observation year) divided by the number of subjects alive and registered in the GPs' lists in the observation year. The cumulative incidence was measured as the number of new users (i.e., at least one prescription without any prescription in the year prior) divided by the number of living subjects free from any antidepressant drug use in the previous year and registered in the GPs' lists in the observation year.

Among incident AD users, we analysed the pattern of AD use over the first year of therapy by drug class. The rate of continuers, intermittent users and discontinuers was calculated in depressed patients specifically. Continuers were defined as patients with a <60 days gap between two consecutive prescriptions. Intermittent users were defined as patients who had a treatment gap of ≥60 days but then received an AD prescription for their first AD of choice. Discontinuers were patients with a treatment gap ≥60 days who did not receive any other AD prescription within the first year of follow-up. An analysis of the drug-switching pattern was carried out for patients who were deemed discontinuers. These analyses on mode of AD use as defined above have been carried out previously for the general population [21].

The Chi-Squared test for categorical variables and Student's *t*-test for continuous variables at a significance level of $p<0.05$ were used for assessing the differences among users of various AD classes. Poisson's regression analysis with 95 % Confidence Intervals (CI) was carried out to identify potential predictors of AD discontinuation among all AD users, and among AD users with depressive disorders specifically. Statistical analyses were performed using STATA 6.0 [22].

Results

Overall, 39,557 AD users ≥65 years old were included in the study (17 % of the total HSD population aged 65 and over). Of these, 24,502 (61.9 %) patients were prescribed SSRIs, 2,200 (5.6 %) were prescribed SNRIs, 1,213 (3.1 %) were prescribed NaSSa, 3,884 (9.8 %) were prescribed TCAs, and 7,759 (19.6 %) were prescribed 'other ADs' (Table 1). Users of different AD classes had a similar mean age (average 75.4 years) and were mostly females (on average, 68 %). A larger proportion of patients over 75 years were prescribed 'other ADs' (4,792 patients; 61.8 % of 'other AD' users) as compared to other drug classes.

The primary indication of use for most ADs appeared to be anxiety disorder followed by depressive disorder, with SSRIs, SNRIs and NaSSAs being most commonly used for these indications (Table 1). A larger proportion of NaSSa (mianserin, mirtazapine) and 'other AD' users had a diagnosis of dementia (8.0 % and 8.6 % respectively) compared to other drug classes. TCAs were commonly prescribed for clinical indications associated with pain such as migraine (5.6 %). All ADs were commonly used in patients diagnosed with cancer and thyroid disorders. A relatively high proportion of TCA users also had a diagnosis of cardiac arrhythmia (8.9 %) while a large number of SSRI users had a diagnosis of cerebrovascular disease (11.1 %). With regards to other drug use within six months of AD prescription, all AD users were most commonly treated with antihypertensive medication (68.2 %), salicylates/ticlopidine (33.8 %) and NSAIDs (35.6 %) (Table 1).

Over seven observation years, AD use increased across all drug classes. The prevalence of SSRI use was higher than any other AD class throughout the observation period, ranging from 102.7 to 195.3 users per 1,000 inhabitants (Fig. 1). The use of paroxetine, citalopram and sertraline, and especially escitalopram increased markedly over seven years (Fig. 2). Paroxetine was the most commonly prescribed SSRI (75.3 per 1,000 inhabitants in 2009), followed by citalopram (70.3 per 1,000 inhabitants in 2009). Duloxetine was introduced later compared to the other AD drugs, but its use increased sharply over a short period of time, from 3.5 to 12.7 per 1,000 inhabitants over 2003-2009. The incident use of SSRIs during the first year of therapy was much higher than any other drug class, varying from 24.6 to 29.6 users per 1,000 inhabitants from 2003 to 2009 (Fig. 3). For each drug class, the incidence rate was rather stable or decreased over the observation period. The highest number of continued prescriptions was seen for SSRIs (N=971; 16.64 % of all incident depressed AD

Table 1 Demographic and clinical characteristics of over 65-year old users with incidence of antidepressants in their first year of drug use, classified by drug class

	SSRI *N*=24,502 (%)	SNRI *N*=2,200 (%)	NaSSa *N*=1,213 (%)	TCA *N*=3,883 (%)	OTHER ADs *N*=7,759 (%)	Total *N*=39,557
Mean age (SD)	75 (6.9)	74 (6.6)	76 (7.2)	74 (6.8)	78 (7.6)	–
Aged over 75	12,024 (49.1)	898 (40.8)	647 (53.3)	1,619 (41.7)	4,792 (61.8)	19,980 (50.5)
Females	16,628 (67.9)	1,488 (67.6)	776 (64.0)	2,685 (69.1)	5,151 (66.4)	26,728 (67.6)
Clinical indication for AD use						
Depressive disorder	5,506 (22.5)	478 (21.7)	202 (16.7)	281 (7.2)	622 (8.0)	7,089 (17.9)
Anxiety disorder	7,741 (31.6)	693 (31.5)	255 (21.0)	480 (12.4)	1,444 (18.6)	10,613 (26.8)
Depression in dementia	1,013 (4.1)	71 (3.2)	97 (8.0)	47 (1.2)	664 (8.6)	1,892 (4.8)
Migraine	78 (0.3)	12 (0.5)	8 (0.7)	219 (5.6)	19 (0.2)	336 (0.8)
Other neuro-psychiatric disorders	1,025 (4.2)	76 (3.5)	100 (8.2)	166 (4.3)	409 (5.3)	1,776 (4.5)
Other or not otherwise specified	1,030 (4.2)	116 (5.3)	110 (9.1)	756 (19.5)	1,167 (15.0)	3,179 (8.0)
Not known	8,109 (33.1)	754 (34.3)	441 (36.3)	1,934 (49.8)	3,434 (44.3)	14,672 (37.1)
Other co-morbidities[a]						
Hypertension	15,536 (63.4)	1,358 (61.7)	741 (61.1)	2,359 (60.8)	4,821 (62.1)	24,815 (62.7)
Dyslipidemia	5,557 (22.7)	512 (23.3)	236 (19.5)	865 (22.3)	1,537 (19.8)	8,707 (22.0)
Type 2 diabetes mellitus	4,381 (17.9)	426 (19.4)	203 (16.7)	664 (17.1)	1,275 (16.4)	6,949 (17.6)
Obesity	3,311 (13.5)	323 (14.7)	125 (10.3)	589 (15.2)	894 (11.5)	5,242 (13.2)
Coronary heart disease	3,414 (13.9)	268 (12.2)	148 (12.2)	425 (10.9)	1,073 (13.8)	5,328 (13.5)
Cerebrovascular disease	2,714 (11.1)	216 (9.8)	129 (10.6)	328 (8.4)	935 (12.1)	4,322 (10.9)
Congestive heart failure	1,015 (4.1)	71 (3.2)	70 (5.8)	137 (3.5)	405 (5.2)	1,698 (4.3)
Cardiac arrhythmia	3,120 (12.7)	232 (10.5)	154 (12.7)	344 (8.9)	1,094 (14.1)	4,944 (12.5)
Peripheral vascular disease	2,742 (11.2)	249 (11.3)	122 (10.1)	451 (11.6)	969 (12.5)	4,533 (11.4)
Chronic renal disease	1,015 (4.1)	59 (2.7)	64 (5.3)	144 (3.7)	367 (4.7)	1,649 (4.2)
Chronic liver disease	1,424 (5.8)	123 (5.6)	57 (4.7)	268 (6.9)	566 (7.3)	2,438 (6.1)
Thyroid disorder	3,275 (13.4)	302 (13.7)	159 (13.1)	505 (13.0)	957 (12.3)	5,198 (13.1)
Cancer	3,899 (15.9)	348 (15.8)	209 (17.2)	747 (19.2)	1,377 (17.7)	6,580 (16.6)
Concomitant drugs acting on the CNS[b]						
Antiparkinson drugs	826 (3.4)	77 (3.5)	101 (8.3)	129 (3.3)	387 (5.0)	1,520 (3.8)
Antiepileptics	1,427 (5.8)	212 (9.6)	109 (9.0)	632 (16.3)	430 (5.5)	2,810 (7.1)
Antipsychotics	1,267 (5.2)	111 (5.0)	153 (12.6)	170 (4.4)	674 (8.7)	2,375 (6.0)
Anxiolytics	6,192 (25.3)	547 (24.9)	331 (27.3)	779 (20.1)	1,769 (22.8)	9,618 (24.3)
Opioids	2,023 (8.3)	232 (10.5)	97 (8.0)	870 (22.4)	686 (8.8)	3,908 (9.9)
Cholinesterase inhibittors	304 (1.2)	18 (0.8)	18 (1.5)	13 (0.3)	192 (2.5)	545 (1.3)
Other drugs[b]						
Salicylates and ticlopidine	8,455 (34.5)	693 (31.5)	383 (31.6)	1,130 (29.1)	2,718 (35.0)	13,379 (33.8)
Other anti-platelet drugs	196 (0.8)	20 (0.9)	10 (0.8)	31 (0.8)	76 (1.0)	333 (0.8)
Anticoagulants	1,226 (5.0)	100 (4.5)	75 (6.2)	116 (3.0)	358 (4.6)	1,875 (4.7)
Antiipertensives	16,941 (69.1)	1,443 (65.6)	816 (67.3)	2,517 (64.8)	5,261 (67.8)	26,978 (68.2)
Cardiac therapy	4,726 (19.3)	320 (14.5)	262 (21.6)	536 (13.8)	1,643 (21.2)	7,487 (18.9)
Immunosuppressants	47 (0.2)	3 (0.1)	4 (0.3)	15 (0.4)	15 (0.2)	84 (0.2)
Corticosteroids	2,504 (10.2)	237 (10.8)	104 (8.6)	646 (16.6)	755 (9.7)	4,246 (10.7)
NSAIDs	8,448 (34.5)	849 (38.6)	360 (29.7)	1,910 (49.2)	2,542 (32.8)	14,109 (35.7)
Charlson Index[a]						
0	9,661 (39.4)	902 (41.0)	471 (38.8)	1,599 (41.2)	2,795 (36.0)	15,428 (39.0)
1-2	11,185 (45.6)	999 (45.4)	551 (45.4)	1,695 (43.7)	3,588 (46.2)	18,0187 (45.5)
3-4	3,039 (12.4)	265 (12.0)	154 (12.7)	466 (12.0)	1,141 (14.7)	5,056 (12.8)
5+	617 (2.5)	34 (1.5)	37 (3.1)	123 (3.2)	235 (3.0)	1,046 (2.6)

Table 1 (continued)

	SSRI *N*=24,502 (%)	SNRI *N*=2,200 (%)	NaSSa *N*=1,213 (%)	TCA *N*=3,883 (%)	OTHER ADs *N*=7,759 (%)	Total *N*=39,557
Number of drugs[b]						
0	2,164 (8.8)	234 (10.6)	111 (9.2)	292 (7.5)	548 (7.1)	3,349 (8.4)
1-4	8,341 (34.0)	725 (33.0)	417 (34.4)	1,212 (31.2)	2,665 (34.3)	13,360 (33.8)
5+	13,997 (57.1)	1,241 (56.4)	685 (56.5)	2,379 (61.3)	4,546 (58.6)	22,848 (57.8)

Other psychiatric disorders: includes personality disorders, psychotic disorder, psychosomatic reaction, acute stress reaction, adjustment disorder and other psychiatric disorders excluding psychosis; Other: includes painful bone and joint disorder, epilepsy, general symptoms, cancer and Parkinson's disease. The ICD-9 codes for all diagnoses is found in the 'Methods' section

NaSSas noradrenergic and specific serotonergic antidepressants; '*Other ADs*' non-selective monoamine oxidase inhibitors (MAOIs), monoamine oxidase A inhibitors and other antidepressants (Anatomic Therapeutic Chemical (ATC) classification: N06AF*, N06AG* and other N06AX* not previously included); *SSRIs* selective serotonin-reuptake inhibitors; *SNRIs* serotonin-noradrenaline reuptake inhibitors; *TCAs* tricyclic antidepressants; *SD* standard deviation; *ADs* antidepressants; *BPSD* behavioural and psychological disorders; *CNS* central nervous system; *NSAIDs* non-steroidal anti-inflammatory drugs

[a] In the period preceding the index date;the method used to calculated the Charlson Index is found in the 'Methods' section

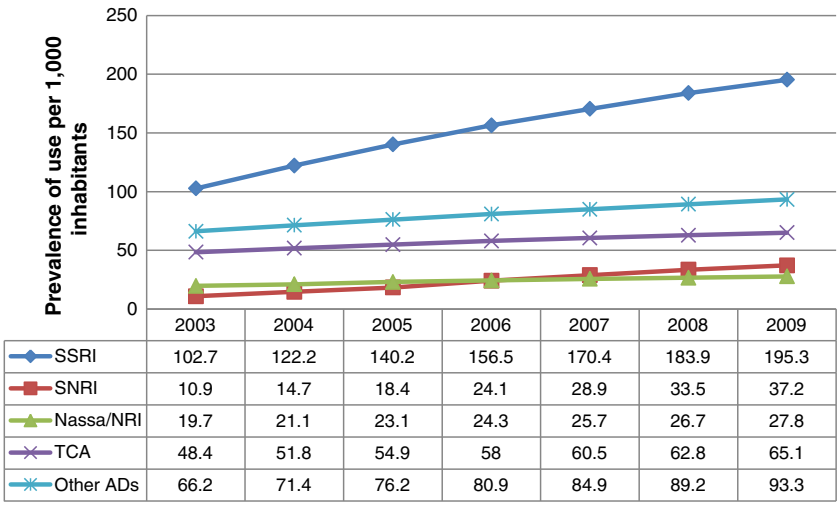
[b] In the six months prior to the index date

users) and the lowest for TCAs (*N*=6; 2.14 % of all incident depressed AD users) (Table 2).

A specific analysis on the risk of AD treatment discontinuation in depressed patients over 65 is reported in Table 3. Patients aged 65-74 were more likely to discontinue AD medication compared to ≥75 year old AD users (Table 3). The co-prescription of opioids in depressed patients within six months of an AD prescription was associated with a higher risk of discontinuation (RR=11.08; CI: 0.98 - 1.19). Older people living in Southern Italy were more likely to discontinue AD treatment as compared to those residing in the rest of Italy (RR=1.09, CI: 1.02 - 1.15). Use of an increasing number of drugs was also associated with discontinuation (RR=1.22, CI: 1.1 - 1.34), as was a higher co-morbidity index (RR=1.07, CI: 0.91 - 1.26). Among SSRIs, escitalopram was least associated with discontinuation (IRR=0.88; CI: 0.8 - 0.97). The use of NaSSas, TCAs and 'other ADs' was associated with AD discontinuation. Our further analysis of switching after AD discontinuation showed that in general, most AD discontinuation was not due to switching AD and that of AD discontinuers who switched AD, most switched to SSRIs.

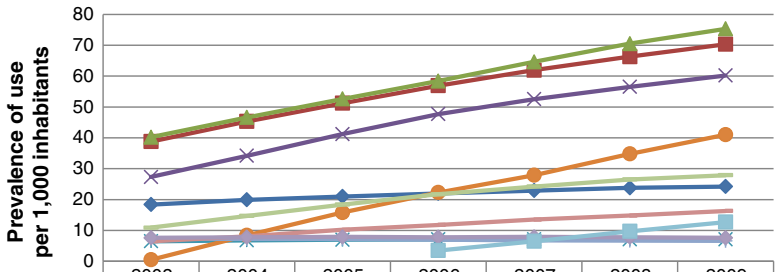
Discussion

To our knowledge, this is the first Italian nationwide population-based study which explored the use of ADs in elderly patients in depth. A nationwide antidepressant pre-



	2003	2004	2005	2006	2007	2008	2009
SSRI	102.7	122.2	140.2	156.5	170.4	183.9	195.3
SNRI	10.9	14.7	18.4	24.1	28.9	33.5	37.2
Nassa/NRI	19.7	21.1	23.1	24.3	25.7	26.7	27.8
TCA	48.4	51.8	54.9	58	60.5	62.8	65.1
Other ADs	66.2	71.4	76.2	80.9	84.9	89.2	93.3

Fig. 1 Prevalence (per 1,000 inhabitants) of antidepressant prescription by drug class in Italian patients over 65 years old from 2003 to 2009

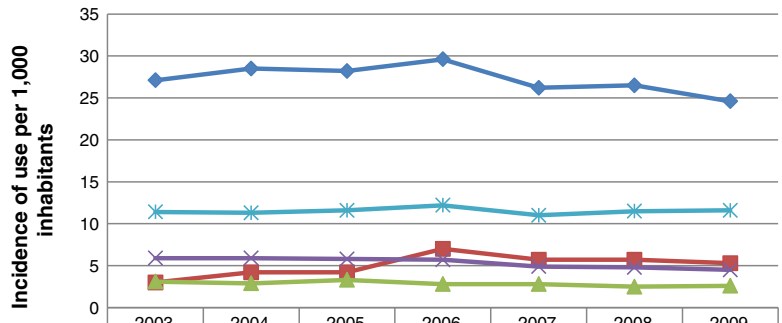


	2003	2004	2005	2006	2007	2008	2009
Fluoxetine	18.4	19.9	21	22	22.9	23.8	24.2
Citalopram	38.8	45.3	51.2	56.9	61.9	66.3	70.3
Paroxetine	40.2	46.6	52.6	58.4	64.6	70.5	75.3
Sertraline	27.3	34.2	41.2	47.7	52.5	56.5	60.2
Fluvoxamine	6.5	6.8	7	7.1	7.1	7.1	7.1
Escitalopram	0.5	8.4	15.8	22.3	27.9	34.8	41
Mianserin	7.4	7.2	7.2	7	6.8	6.7	6.6
Mirtazepine	6.5	8.1	10.2	11.8	13.5	14.8	16.3
Venlafaxine	10.9	14.7	18.4	21.7	24.2	26.5	27.9
Reboxetine	7.6	7.8	7.9	7.8	7.9	7.8	7.6
Duloxetine				3.5	6.5	9.7	12.7

Fig. 2 Prevalence (per 1,000 inhabitants) of SSRI, SNRI and NaSSa prescription in Italian patients over 65 years old from 2003 to 2009

scribing study has been carried out using HSD but this did not focus on elderly patients [21]. This study found that the prevalence of AD use in older patients increased every year without a corresponding increase in incident use during the first year of therapy. This is in agreement with a previous observational study investigating AD use in the elderly in a Lombardy general practice setting [9]. The reason for a lack of increasing incident AD use could be a chronic but intermittent use of ADs particularly for short-term indications such as migraine or neuropathic pain or the repetition of AD treatment in the case of symptomatic relapse in older patients who have not been successfully treated.

In line with previous studies, women and very old patients were more likely to be treated with ADs [6, 9, 23]. SSRIs were most commonly prescribed (61.9 % of all AD users) as a first choice AD, a trend identified both in Italy and internationally [6, 23-25]. The rationale for the increased prescription of escitalopram in primary care might be associated with its known lower propensity for drug-drug interactions as well as potential commercial influence [26]. It is possible that SSRIs are so widely used because their variety of clinical indications [6]. SSRIs are not necessarily more effective than other ADs, but may still be prescribed more frequently than other ADs due to better tolerability and overall favourable



	2003	2004	2005	2006	2007	2008	2009
SSRIs	27.1	28.5	28.2	29.6	26.2	26.5	24.6
SNRIs	3	4.2	4.2	7	5.7	5.7	5.3
NaSSas/NRIs	3.1	2.9	3.3	2.8	2.8	2.5	2.6
TCAs	5.9	5.9	5.8	5.7	4.9	4.8	4.5
Other ADs	11.4	11.3	11.6	12.2	11	11.5	11.6

Fig. 3 Cumulative incidence (per 1,000 patients) of antidepressant drug prescription in the first year of drug use by class in Italian patients over 65 years old from 2003 to 2009

Table 2 Persistence to the antidepressant treatment in elderly patients with depressive disorder over the first year of follow-up

	Frequency of type of use [*N* (% of total incident use)]		
Drug of first choice	Continuers	Intermittent users	Discontinuers
TOTAL [*N*=39,560]*	[*N*=1,257 (17.73)]	[*N*=1,921 (27.10)]	[*N*=3,911 (55.17)]
SSRI [*N*=24,504]*	[*N*=971 (16.64)]	[*N*=1,289 (23.41)]	[*N*=3,246 (58.95)]
SNRI [*N*=2,200]*	[*N*=71 (14.85)]	[*N*=76 (15.90)]	[*N*=331 (69.25)]
NaSSa [*N*=1,213]*	[*N*=26 (12.87)]	[*N*=51(25.25)]	[*N*=125 (61.88)]
TCA [*N*=3,884]*	[*N*=6 (2.14)]	[*N*=110 (39.15)]	[*N*=165 (58.72)]
Other ADs [*N*=7,759]*	[*N*=22 (3.54)]	[*N*=151 (24.28)]	[*N*=449 (72.19)]

SSRIs selective serotonin-reuptake inhibitors; *SNRIs* serotonin-noradrenaline reuptake inhibitors; *NaSSas* noradrenergic and specific serotonergic antidepressants; *TCAs* tricyclic antidepressants; '*Other ADs*' non-selective monoamine oxidase inhibitors (MAOIs), monoamine oxidase A inhibitors and other antidepressants (Anatomic Therapeutic Chemical (ATC) classification: N06AF*, N06AG* and other N06AX* not previously included)

*Refers to the number of incident users of the drug of first choice

risk-benefit ratio [25]. Accordingly, this study shows that SSRIs had the highest proportion of continuous users with respect to the other AD classes, overall and in depressed patients specifically, in line with other studies [23]. Despite the good safety profile of SSRIs, an association between SSRI use and cerebrovascular disease has been found [27]. Nevertheless, 11 % of elderly patients using SSRIs in this study had a pre-existing diagnosis of cerebrovascular disease.

In this study, SSRIs were most commonly prescribed in patients with anxiety and depressive disorders, in agreement with previous studies [4, 6]. This study also found that SSRIs were frequently co-prescribed with antihypertensive agents, NSAIDs and salicylates. A general concern about widespread SSRI use is the risk of bleeding, particularly due to concomitant treatment with antiplatelet (e.g., low dose aspirin) and anticoagulant drugs as well as NSAIDs, and the risk of hyponatraemia, particularly due to concomitant use of antihypertensive agents such as diuretics [26].

A cluster of SSRIs (citalopram, paroxetine, sertraline and escitalopram) were found to be most commonly prescribed. Paroxetine, citalopram and/or escitalopram were also commonly prescribed in the general population [4, 6, 9, 24]. A meta-analysis comparing SSRIs reported that fluvoxamine and fluoxetine have a lower tolerability compared to other SSRIs [28]. This may be due to the comparatively higher risk of adverse drug events, since these two drugs had among the highest drop-out rates in randomised clinical trials (up to 70 % and 45 % respectively) [29].

The use of TCAs in this study was much lower than SSRIs, as reported elsewhere [9, 24]. It appears that TCAs were used more commonly in pain-related disorders than in depressive disorder, as supported by the higher use of opioid analgesics (22.4 %) and NSAIDs (49.2 %) in TCA users. It was alarming to note that TCAs were prescribed in elderly patients with cardiac arrhythmia (8.9 %), as cardiotoxicity is a known adverse effect of TCAs. Other antidepressants such as citalopram and escitalopram have also been recently implicated in increased risk of arrhythmia [30, 31]. However, drug safety warnings regarding these two drugs were issued after the end of the observation period and for this reason could not have affected prescribing rates.

There were higher proportions of NaSSas and 'other ADs' in dementia. This may be explained considering that NaSSas such as mirtazepine and other ADs such as trazodone have sedating properties and might be prescribed off-label in clinical practice to treat insomnia as well as agitation in the elderly [32, 33], as found elsewhere [6]. Recent evidence comparing the use of mirtazapine and sertraline, another AD that was even more commonly prescribed in this study, found that neither drug is more effective than placebo in treating depressive disorder in dementia and suggested that their use in this context should be reconsidered [34].

Depressed patients were more likely to discontinue their ADs if prescribed any AD other than SSRI, if they had a higher co-morbidity index and if they were co-prescribed more than one drug. The rate of AD discontinuation during the first year of incident therapy was high (55 %) and could generally not be explained by AD switching. This is a significant finding given that the WHO suggests a treatment period of at least 9-12 months for depressive symptoms [14].

The discontinuation rate was higher than reported elsewhere but this is unsurprising as this study considered AD discontinuation over one year while other studies considered discontinuation over much shorter periods such as 30 days and eight weeks [35, 36]. In particular, the discontinuation rate was higher than that found in a recent Italian nationwide study, where 28 % of AD users (378 out of 1,377 AD users) discontinued their medication within the first year of AD treatment [4]. The authors of this active monitoring study indicated that the lower discontinuation rate was expected as a result of stronger motivation of the prescribers to closely monitor patients starting AD therapy, thus, favouring

Table 3 Risk factors of antidepressant treatment discontinuation during the first year of therapy in elderly patients, in all AD users and in depressed patients only

	All users Relative risk (95 % CI)	Users with depression Relative risk (95 % CI)
Age		
65-74	1.0	1.0
75+	0.96 (0.94 - 0.98)	0.94 (0.89 - 0.99)
Gender		
Males	1.0	1.0
Females	0.99 (0.97 - 1.01)	0.99 (0.94 - 1.05)
Geographical area		
North Italy	1.0	1.0
Central Italy	0.96 (0.93 - 0.99)	0.95 (0.88 - 1.02)
South Italy	1.07 (1.04 - 1.1)	1.09 (1.02 - 1.15)
Antidepressant agents		
Citalopram	1.0	1.0
Fluoxetine	1.12 (1.04 - 1.19)	1.1 (0.96 - 1.27)
Paroxetine	0.98 (0.94 - 1.02)	1 (0.93 - 1.09)
Sertraline	0.94 (0.9 - 0.97)	0.93 (0.86 - 1.01)
Fluvoxamine	0.96 (0.82 - 1.12)	0.8 (0.53 - 1.2)
Escitalopram	0.89 (0.85 - 0.93)	0.88 (0.8 - 0.97)
Duloxetine	1.13 (1.02 - 1.24)	1.16 (0.93 - 1.43)
Venlafaxine	1.18 (1.11 - 1.25)	1.22 (1.08 - 1.39)
Mianserin	1.61 (1.38 - 1.87)	1.6 (1.06 - 2.42)
Mirtazapine	1.17 (1.08 - 1.26)	1.1 (0.91 - 1.32)
TCA	1.83 (1.75 - 1.91)	1.68 (1.48 - 1.92)
Other ADs	1.91 (1.85 - 1.98)	1.9 (1.72 - 2.1)
Concomitant CNS medication[a]		
Anti-Parkinson drugs	0.8 (0.76 - 0.85)	0.73 (0.61 - 0.87)
Antiepileptic drugs	0.92 (0.88 - 0.96)	0.88 (0.78 - 0.99)
Antipsychotic drugs	0.87 (0.83 - 0.91)	0.88 (0.78 - 0.99)
Anxiolytic agents	0.93 (0.9 - 0.95)	0.92 (0.87 - 0.98)
Opioids	1.04 (1 - 1.08)	1.08 (0.98 - 1.19)
Cholinesterase inhibitors	0.75 (0.68 - 0.83)	0.6 (0.41 - 0.87)
Charlson Index[b]		
0	1.0	1.0
1-2	0.97 (0.95 - 0.99)	0.97 (0.92 - 1.03)
3-4	0.98 (0.94 - 1.01)	0.94 (0.86 - 1.02)
5+	1 (0.93 - 1.07)	1.07 (0.91 - 1.26)
Number of drugs[a]		
0	1.0	1.0
1-4	1.16 (1.11 - 1.21)	1.22 (1.1 - 1.34)
5+	1.15 (1.11 - 1.2)	1.22 (1.1 - 1.34)

relative risk was calculated using Poisson regression analysis

ADs antidepressants; *CNS* central nervous system

Other drugs: non-selective monoamine oxidase inhibitors (MAOIs), monoamine oxidase A inhibitors and other antidepressants (Anatomic Therapeutic Chemical (ATC) classification: N06AF*, N06AG* another N06AX* not previously included); TCAs: tricyclic a ntidepressants

AD users were considered as discontinuers if there was a gap larger than 60 days after the end of the last prescription during the first year of treatment

[a] In the six months prior to the index date

[b] In the period preceding the index date; the method used to calculated the Charlson Index is found in the 'Methods' section

increased persistence to the drug treatment. The overall discontinuation rate that emerged from our study (55 %) is however much lower than that of a retrospective study also conducted using Italian HSD nationwide data. This study found that only 13 % of patients from the general population over 17 years old were continuous AD users [21].

Discontinuation might arise if the patient's condition is mild or resolves itself, as might be the case in mild depression. A high drug burden also contributes to discontinuation. Among AD users, the concomitant use of >5 drugs was more likely to predict discontinuation. The use of NaSSas, TCAs and 'other ADs' was also more likely to predict discontinuation in depressed patients, possibly as a result of lower tolerability as compared to SSRI. Patients' origins in Southern Italy were also predictive of discontinuation. Reasons for this might include a less

effective collaboration between GPs and psychiatric services in Southern Italy as compared to other parts of the country. These patients should, therefore, be monitored more carefully. In the case of TCAs, use in pain-related indications such as post-herpetic neuralgia or acute lower back pain may justify short-term use [37].

This study had several strengths as well as limitations. It included a large number of patients (39,557 AD users) on a national scale, providing insight into real AD prescribing patterns in elderly Italian patients at the primary care level. We also extended our analysis of discontinuation trends to include switchers which provided added insight into the context of AD discontinuation. The cohort was well-characterized in terms of co-morbidities and primary indication of AD use, both of which are not commonly recorded in similar clinical research [23, 24], including other research using the HSD [9] and which are essential in the interpretation of results regarding AD use.

However, some limitations warrant caution. Although this study was conducted using detailed patient and prescription data, some clinical data such as the indication of AD use was not always available. In addition, the AD exposure was obtained from prescription records, and it is possible that the prescriptions were not filled or that, if filled, there was low compliance to the therapeutic regimen. As the prescription data reflects only reimbursement data, it is possible that the prevalence of use is underestimated, particularly if patients purchase the ADs themselves from the private healthcare sector [23, 24]. However, this scenario is unlikely as all ADs (apart from agomelatine which was marketed after the end of the study period) are reimbursed by NHS, irrespective of the indication of use. We did not collect data on the dose prescribed, a factor which may influence persistence rates because doses that are too high may prompt adverse drug reactions while doses that are too low may not be effective, in both cases precipitating discontinuation. The prescribers were not specialists, and as a result the recorded psychiatric indications for use may not be very detailed or precise. Patients who were institutionalized (i.e., admitted in nursing homes) are in most cases still cared for by GPs and as such, AD prescriptions can still be traced. On the other hand, the database used cannot capture prescription data for patients who are hospitalized and this might lead to over-estimation of discontinuation rates. However, only a long stay in the hospital (≥60 days) would have a significant impact on the results (we considered discontinuers as those AD users with a gap ≥60 days between two consecutive AD prescriptions), which is not likely to be a common occurrence. In addition, we found that very old patients (≥75 years) are less likely to discontinue ADs as compared to their younger counterparts (65-74 years). As the oldest patients are more likely to have longer hospital admissions, this finding would suggest that lack of hospital data in our study has no significant effects on AD discontinuation rates. On the other hand, the high discontinuation rates found in our study should be interpreted in the context of the larger population compared to other studies. It is more likely to find patients who are discontinuers or have a short-term indication of use in a large population. Finally, we were not able to further analyse the context of AD discontinuation other than switching, e.g., because symptoms resolved, as we did not have data on this outcome.

Conclusion

ADs, especially SSRIs, are widely and increasingly prescribed in elderly Italian patients. We found high AD discontinuation rates in elderly depressed patients, which is likely to impact negatively on the achievement of therapeutic endpoints. We identified depressed patients who receive multi-drug therapy, use specific ADs such as TCAs and patients that live in Southern Italy as those having higher risk of AD discontinuation, thus suggesting that these patients should be monitored more closely to improve clinical and economic benefits of AD treatment.

Conflict of interest All authors have no conflicts of interests to declare.

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