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Research paper

Antidepressant use in Denmark, Germany, Spain, and Sweden between 2009 and 2014: Incidence and comorbidities of antidepressant initiators

Joan Forns[a,*], Anton Pottegård[b], Tammo Reinders[c], Beatriz Poblador-Plou[d], Rosa Morros[e,f,g], Lena Brandt[h], Miguel Cainzos-Achirica[a], Maja Hellfritzsch[b], Tania Schink[c], Alexandra Prados-Torres[d], Maria Giner-Soriano[e,f,g], David Hägg[h], Jesper Hallas[b], Jordi Cortés[e,f,g,i], Emmanuelle Jacquot[j], Nicolas Deltour[j], Susana Perez-Gutthann[a], Manel Pladevall[a], Johan Reutfors[h]

[a] Epidemiology, RTI Health Solutions, Barcelona, Spain
[b] Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark
[c] Leibniz Institute for Prevention Research and Epidemiology–BIPS, Bremen, Germany
[d] EpiChron Research Group on Chronic Diseases, Aragon Health Sciences Institute (IACS), IIS Aragón, REDISSEC ISCIII, Miguel Servet University Hospital, Zaragoza, Spain
[e] Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain
[f] Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain
[g] Institut Català de la Salut, Barcelona, Spain
[h] Centre for Pharmacoepidemiology, Department of Medicine, Solna, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
[i] Universitat Politècnica de Catalunya, Departament d'Estadística i Investigació Operativa, Barcelona, Spain
[j] Pharmacoepidemiology Department, Les Laboratoires Servier, Suresnes, France

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ABSTRACT

Background: We aimed to describe patterns of use and characteristics of 10 commonly used antidepressants for the period 2009–2014 in Denmark, Germany, Spain, and Sweden.

Methods: Adult initiators from 2009 to 2014 of each study antidepressant were identified in four countries using five data sources: the Danish National registers, GePaRD (Germany), EpiChron (Aragon, Spain), SIDIAP (Catalonia, Spain), and the Swedish National Registers. The study included 10 study antidepressants: citalopram, escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, venlafaxine, amitriptyline, mirtazapine, and agomelatine.

Results: Citalopram was the most prescribed study antidepressant, followed by mirtazapine. Paroxetine and agomelatine were the least prescribed antidepressants. Mirtazapine was widely used among older antidepressant initiators with higher percentages of comorbidities at baseline, and fluoxetine was used among young patients. Citalopram and amitriptyline had the lowest percentage of multiple antidepressant use in the 12 months prior to the current treatment episode, while agomelatine, duloxetine, and venlafaxine had the highest percentage of multiple antidepressant use in the year prior to the current treatment episode.

Limitations: The most important limitations are exposure information based on filled prescriptions, focus on antidepressant initiators only, lack of information on the indication, and heterogeneity of the type of data across data sources.

Conclusions: Results of this study including 4.8 million study antidepressant initiators of study antidepressants suggest that citalopram and mirtazapine are the most commonly prescribed antidepressants. Agomelatine and paroxetine were the least used antidepressants in the participating populations. Mirtazapine was the antidepressant most commonly prescribed among older antidepressant initiators with high percentage of comorbidities at baseline, whereas fluoxetine was commonly used among young patients.

* Corresponding author.
E-mail address: jforns@rti.org (J. Forns).

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1. Introduction

Antidepressants are among the most prescribed drugs in Europe. Besides depression as the major indication, antidepressants are also used for a wide range of other conditions such as panic disorders, generalized anxiety disorder, and neuropathic pain (Noordam et al., 2015). The most recent drug utilization studies conducted in Europe suggest an increase in the use of antidepressants over time, particularly for selective serotonin reuptake inhibitors (SSRIs), the most commonly prescribed type of antidepressant class (Abbing-Karahagopian et al., 2014; Bauer et al., 2008; Noordam et al., 2015; Poluzzi et al., 2013).

In past decades, the number of antidepressants available on the market has increased markedly, resulting in a great variety of treatment options for prescribers. The choice of an antidepressant is influenced by several factors, including those specifically related to the drug profile (e.g. side effects, tolerability, and cost), physician characteristics (e.g. specialty, country of practice), reimbursement policies (Bauer et al., 2008), and patient characteristics, such as severity of depression and presence of comorbidities (Jobski et al., 2017b; Zimmerman et al., 2004).

With the exception of one German study restricted to adults older than 65 years (Jobski et al., 2017b), no studies have analysed the use of antidepressants in adults from the general population in several European countries since 2012. Also, little information is available on the patterns of comorbidities among initiators of different antidepressant drugs. Therefore, we aimed to describe the cumulative incidence of initiators of 10 commonly prescribed antidepressants for the period 2009–2014 in Denmark, Germany, Spain, and Sweden. We also aimed to compare the characteristics of initiators of each of the 10 study antidepressants in terms of their demographic characteristics, presence of comorbidities, health care resource use, and patterns of use.

2. Methods

2.1. Study setting

This drug utilization study was conducted using data collected during a postauthorisation safety study investigating the potential risk of acute hepatoxic reactions associated with the use of agomelatine and other antidepressants (Pladevall, 2018). Initiators of each study antidepressant were identified in four countries using five automated health data sources: the Danish National Health Registers (Denmark) (Pottegard et al., 2016; Schmidt et al., 2015), the German Pharmacoepidemiological Research Database (GePaRD) (Germany) (Jobski et al., 2017a,b; Pigeot and Ahrens, 2008), the EpiChron Cohort from Aragon Health Sciences Institute (Aragon, Spain) (Prados-Torres et al., 2018), the Information System for Research in Primary Care (SIDIAP) (Catalonia, Spain) (SIDIAP, 2014), and the Swedish National Registers (Sweden) (Ludvigsson et al., 2011; Wettermark et al., 2007). The main characteristics of each database are described in Supplementary Table 1. The study period in each data source started after the launch of agomelatine in each respective country (2009 or 2010) and ended on the last year for which data was available in each data source (2013 or 2014).

2.2. Study population

The study cohort included all adult initiators of any of the 10 relevant antidepressants in the study databases from 2009 to 2014 with at least 12 months of continuous enrolment in the data source. The study cohort included all individuals aged 18 years or older at the date of the first-recorded prescription fill for any of the study antidepressants during the study period(s) with no prescription fill for the same study antidepressant within the prior 12 months (initiators). One patient could contribute to several antidepressant groups if eligibility criteria were accomplished. For women, pregnancy at the start date of antidepressant use was an exclusion criterion.

2.3. Study antidepressants

The selected study antidepressants included five SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, and sertraline), two serotonin-norepinephrine reuptake inhibitors (SNRIs) (duloxetine and venlafaxine), one tricyclic antidepressant (TCA) (amitriptyline), one noradrenaline and specific serotonergic antidepressants (NASSAs) (mirtazapine), and one melatonergic agonist and 5-HT2C antagonist (agomelatine) (Supplementary Table 2). These antidepressants were selected in the agomelatine postauthorisation safety study to represent (1) the most commonly used antidepressants in the participating countries and (2) different classes of antidepressants. Agomelatine was selected for regulatory reasons as the main exposure of interest (Pladevall, 2018). Specific details on the exposure definition are included in Supplementary Methods. Indication of use of study antidepressants for the study population was not available.

2.4. Characterisation of initiators of study antidepressants

Initiators of the study antidepressants were characterised at the date of their first prescription according to age and sex. Comorbidity information at any time before cohort inclusion was ascertained through hospital discharge diagnoses and diagnoses reported in primary care, when available, in combination with information on the use of medications for specific diseases when applicable (Pladevall, 2018). Information on hospitalisations during the 12 months prior to the current treatment episode was also collected as a measure of health care utilisation.

Patterns of antidepressant use were also assessed. First, we measured the recent use of any antidepressant (N06A group) available on the market at the time of the study (0, 1, 2, or more) in the 12 months prior to the current treatment episode. Switching and multiple uses were not differentiated but rather combined into a single variable. We also measured the duration of the first treatment episode of current use (in months). Finally, we measured whether the study antidepressants were prescribed alone or combined with other antidepressants by calculating the percentage of treatment episodes of current use with combined use of another antidepressant.

2.5. Statistical analyses

Data describing the study population and prescribing patterns of antidepressants are presented as means, standard deviations, frequencies, or percentages, as appropriate. The estimated cumulative incidence of antidepressant initiation at the end of the study period was calculated overall and for each antidepressant by dividing the total number of initiators and the number of initiators for each study antidepressant during the study period (2009–2013/2014) by the total reference adult population in each data source at the end of 2013 or 2014 (depending on the end of the study period). Stata (version 14) or SAS (version 9.4 or later) was used for the analyses by the different study research partners evaluating each of the individual data sources.

3. Results

The study included a total of 4,833,774 initiators of antidepressants (Table 1). Sweden had the largest population with 1.8 million initiators of study antidepressants, followed by GePaRD (Germany) with 1.7 million, Denmark with 0.8 million, and the Spanish populations (EpiChron [Aragon] and SIDIAP [Catalonia]) with less than 0.3 million each.

Table 1
Number of study antidepressant initiators with age and sex distribution.

	Denmark	GePaRD, Germany	EpiChron, Aragon, Spain	SIDIAP, Catalonia, Spain	Sweden
Study period					
Number of study antidepressant initiators, *n* (%)					
Citalopram	253,531 (30%)	463,794 (27%)	10,412 (5%)	53,076 (20%)	405,944 (22%)
Escitalopram	57,184 (7%)	77,765 (5%)	52,256 (25%)	29,429 (11%)	141,701 (8%)
Fluoxetine	18,448 (2%)	66,782 (4%)	17,045 (8%)	23,784 (9%)	77,044 (4%)
Paroxetine	18,968 (2%)	50,141 (3%)	26,213 (12%)	38,883 (15%)	34,666 (2%)
Sertraline	137,644 (16%)	88,200 (5%)	12,899 (6%)	28,101 (11%)	359,636 (20%)
Duloxetine	37,514 (4%)	79,456 (5%)	23,744 (11%)	13,509 (5%)	86,454 (5%)
Venlafaxine	87,390 (10%)	147,580 (9%)	11,951 (6%)	15,577 (6%)	130,716 (7%)
Amitriptyline	39,404 (5%)	309,377 (18%)	22,716 (11%)	33,870 (13%)	204,078 (11%)
Mirtazapine	167,020 (20%)	370,741 (22%)	23,971 (11%)	20,324 (8%)	347,596 (19%)
Agomelatine	21,941 (3%)	62,009 (4%)	10,077 (5%)	4167 (2%)	19,046 (1%)
Total	839,044	1,715,845	211,284	260,720	1,806,881
Women (%)					
Citalopram	61%	67%	69.2%	70.4%	65.3%
Escitalopram	61%	66.7%	69.1%	67.1%	64.9%
Fluoxetine	69.9%	72.2%	75.2%	75%	73.5%
Paroxetine	60.5%	65.7%	71.5%	70.3%	60.5%
Sertraline	62.4%	67%	67.2%	69.8%	63.6%
Duloxetine	65.1%	69.3%	73.7%	75.1%	65.6%
Venlafaxine	61.1%	65.9%	69.5%	70.2%	60.6%
Amitriptyline	65.3%	71.8%	74.6%	75.7%	69%
Mirtazapine	57.5%	65.9%	65.5%	64.7%	58.5%
Agomelatine	65%	68.3%	69.7%	67.4%	62.1%
Age, median (IQR), years					
Citalopram	51 (36–70)	54 (42–70)	63 (46–79)	55 (41–71)	56 (39–75)
Escitalopram	52 (37–69)	51 (39–63)	56 (42–73)	51 (38–67)	44 (32–59)
Fluoxetine	41 (29–54)	47 (36–57)	50 (39–63)	47 (37–59)	38 (26–51)
Paroxetine	44 (34–59)	49 (37–60)	53 (40–68)	49 (37–63)	45 (32–58)
Sertraline	44 (31–59)	52 (41–65)	62 (44–78)	61 (44–76)	43 (30–60)
Duloxetine	48 (37–60)	57 (47–70)	59 (46–73)	56 (45–68)	48 (37–61)
Venlafaxine	45 (33–57)	51 (40–61)	55 (43–70)	53 (42–67)	44 (32–58)
Amitriptyline	51 (41–65)	58 (47–71)	53 (40–67)	52 (39–65)	55 (43–68)
Mirtazapine	54 (40–72)	58 (47–73)	67 (49–81)	60 (45–76)	58 (41–76)
Agomelatine	46 (36–57)	52 (42–61)	54 (42–67)	51 (41–62)	45 (33–56)

IQR = interquartile range.

3.1. Demographic characteristics of antidepressant initiators

Women comprised the majority of initiators for all antidepressants (Table 1). The study antidepressant with the highest proportion of women initiators was fluoxetine (>70% in four of five populations). In general, fluoxetine was prescribed to younger patients (median age range, 38 years in Sweden to 50 years in Aragon [Spain]), and mirtazapine was consistently prescribed to older patients (median range, 54 years in Denmark to 67 years in Aragon [Spain]). Among SSRIs, citalopram was commonly prescribed among older patients (range, 51 years in Denmark to 63 years in Aragon [Spain]).

3.2. Incidence of antidepressant initiation

The highest total cumulative incidence of antidepressant initiation for the 10 antidepressants (as per 1000 population) during the period 2009 and 2013/2014 (depending on data source) was found in Sweden with 234, followed by Denmark, 213; Aragon (Spain), 192; Catalonia (Spain), 187; and Germany, 162 (Table 2). Overall, citalopram was the most prescribed study antidepressant, except in Aragon (Spain), with a cumulative incidence ranging from 10 per 1000 population in Aragon (Spain) to 65 per 1000 population in Denmark. In Aragon (Spain), the most prescribed study antidepressant was escitalopram, with a cumulative incidence of 48 per 1000 population. For the other SSRIs, we observed higher rates for sertraline in Denmark and Sweden when compared with other populations. In contrast, rates for fluoxetine and paroxetine were higher in Aragon and Catalonia populations than in the other populations. The use of duloxetine and venlafaxine was similar in all populations, with a higher cumulative incidence for venlafaxine when compared with that for duloxetine, except in Aragon (Spain).

Table 2
Cumulative incidence of study antidepressant initiation at the end of study period (per 1000 population).

	Denmark[a]	GePaRD, Germany[b]	EpiChron, Aragon, Spain[c]	SIDIAP, Catalonia, Spain[a]	Sweden[a]
Citalopram	64.5	43.7	9.5	38.0	52.5
Escitalopram	14.5	7.3	47.5	21.1	18.3
Fluoxetine	4.7	6.3	15.5	17.0	10.0
Paroxetine	4.8	4.7	23.8	27.8	4.5
Sertraline	35.0	8.3	11.7	20.1	46.5
Duloxetine	9.5	7.5	21.6	9.7	11.2
Venlafaxine	22.2	13.9	10.9	11.1	16.9
Amitriptyline	10.0	29.2	20.6	24.2	26.4
Mirtazapine	42.5	35.0	21.8	14.5	45.0
Agomelatine	5.6	5.9	9.2	3.0	2.5
Total	**213.3**	**161.8**	**192.0**	**186.5**	**233.8**

Note: The estimated cumulative incidence of study antidepressant initiation at the end of the study period was calculated by dividing the total number of initiators during the study period (2009–2013/2014) of each antidepressant by the total reference adult population in each data source at the end of 2013 or 2014 (depending on the end of the study period).

[a] Population reference: adult population in the data source at 01 January 2014.

[b] Population reference: average of the adult population average between the size of the source population at the start of the study period (2009) and the end of the study period (2013).

[c] Population reference: adult population in the data source at 01 January 2013.

Table 3
Comorbid conditions among study antidepressant initiators.

	SSRIs,% (95% CI)					SNRIs,% (95% CI)		TCA,% (95% CI)	NASSA,% (95% CI)	Other,% (95% CI)	
	Citalopram	Escitalopram	Fluoxetine	Paroxetine	Sertraline	Duloxetine	Venlafaxine	Amitriptyline	Mirtazapine	Agomelatine	Overall
Denmark (n = 839,044)											
Hypertension	33.3 (32.1–34.5)	32.8 (31.6–34.0)	20 (19.0–21.0)	25.1 (24.0–26.2)	25.1 (24.0–26.2)	30.2 (29.0–31.4)	24.5 (23.4–25.6)	37.6 (36.3–38.9)	36.6 (35.3–37.9)	27.0 (25.9–28.1)	31.1 (29.9–32.3)
Diabetes	8.4 (7.8–9.0)	7.9 (7.3–8.5)	5.5 (5.0–6.0)	6 (5.5–6.5)	6.7 (6.1–7.3)	8.6 (8.0–9.2)	6.7 (6.1–7.3)	10.7 (10.0–11.4)	8.6 (6.0–9.2)	7.2 (6.6–7.8)	7.9 (7.3–8.5)
Hyperlipidaemia	22.3 (21.3–23.3)	21.5 (20.5–22.5)	13.4 (12.6–14.2)	16.8 (15.9–17.7)	17.1 (16.2–18.0)	20.9 (19.9–21.9)	17 (16.1–17.9)	25.7 (24.6–26.8)	24.3 (23.2–25.4)	19.3 (18.4–20.2)	20.9 (19.9–21.9)
Obesity	7.3 (6.7–7.9)	6.7 (6.1–7.3)	10.4 (9.7–11.1)	7.6 (7.0–8.2)	8.4 (7.8–9.0)	11.4 (10.7–12.1)	9.7 (9.0–10.4)	11.4 (10.7–12.1)	6.4 (5.9–6.9)	11.7 (11.0–12.4)	8.1 (7.5–8.7)
History of cerebral arterial disease	10.9 (10.2–11.6)	10.9 (10.2–11.6)	3.7 (3.3–4.1)	5.0 (4.5–5.5)	5.8 (5.3–6.3)	6.3 (5.8–6.8)	5.2 (4.7–5.7)	9.3 (8.6–10.0)	10.4 (9.7–11.1)	5.0 (4.5–5.5)	8.6 (8.0–9.3)
History of ischaemic heart disease	10.4 (9.7–11.1)	10.6 (9.9–11.3)	5.3 (4.8–5.8)	7.0 (6.4–7.6)	7.6 (7.0–8.2)	8.5 (7.9–9.1)	6.9 (6.3–7.5)	11.5 (10.8–12.2)	11.7 (11.0–12.4)	7.6 (7.0–8.2)	9.6 (8.9–10.2)
Chronic pulmonary disease	9.5 (8.8–10.2)	9.3 (8.6–10.0)	8.2 (7.6–8.8)	8.5 (7.9–9.1)	8.6 (8.0–9.2)	9.4 (8.7–10.1)	8.5 (7.9–9.1)	11.8 (11.1–12.5)	10.8 (10.1–11.5)	9.0 (8.4–9.6)	9.5 (8–9–10.2)
Dementia	2.6 (2.3–2.9)	3.4 (3.0–3.8)	0.6 (0.4–0.8)	0.6 (0.4–0.8)	1.5 (1.2–1.8)	1.1 (0.9–1.3)	0.8 (0.6–1.0)	1.1 (0.9–1.3)	3.4 (3.0–3.8)	0.7 (0.5–0.9)	2.2 (1.9–2.5)
GePaRD, Germany (n = 1,715,845)											
Hypertension	57 (55.9–58.1)	52.3 (51.2–53.4)	45.2 (44.2–46.2)	50.3 (49.2–51.4)	55.0 (53.9–56.1)	66.8 (65.6–68.0)	52.7 (51.6–53.8)	63.0 (61.8–64.2)	63.0 (61.8–64.2)	55.3 (54.2–56.4)	58.4 (57.3–59.6)
Diabetes	18.8 (18.2–19.4)	16.3 (15.7–16.9)	13.3 (12.8–13.8)	13.9 (13.3–14.5)	17.9 (17.3–18.5)	26.7 (25.9–27.5)	15.8 (15.2–16.4)	20.6 (19.9–21.3)	20.5 (19.8–21.2)	16.1 (15.5–16.7)	19.0 (18.4–19.7)
Hyperlipidaemia	45.1 (44.1–46.1)	41.4 (40.4–42.4)	35.9 (35.0–36.8)	39.2 (38.3–40.1)	43.7 (42.7–44.7)	53.2 (52.1–54.3)	41.7 (40.7–42.7)	49.9 (48.8–51.0)	50.0 (48.9–51.1)	43.7 (42.7–44.7)	46.3 (45.3–47.3)
Obesity	24.9 (24.2–25.6)	23.2 (22.5–23.9)	28.3 (27.5–29.1)	22.9 (22.2–23.6)	26.0 (25.2–26.8)	34.1 (33.2–35.0)	25.7 (24.9–26.5)	27.9 (27.1–28.7)	24.0 (23.3–24.7)	27.2 (26.4–28.0)	25.9 (25.1–26.6)
History of cerebral arterial disease	9.7 (9.2–10.2)	8.6 (8.2–9.0)	4.3 (4.0–4.6)	5.1 (4.8–5.4)	8.3 (7.9–8.7)	9.2 (8.7–9.7)	6.5 (6.1–6.9)	7.5 (7.1–7.9)	10.1 (9.6–10.6)	5.8 (5.4–6.2)	8.5 (8.0–8.9)
History of ischaemic heart disease	22.7 (22.0–23.4)	19.9 (19.2–20.6)	14.0 (13.4–14.6)	17.8 (17.2–18.4)	21.4 (20.7–22.1)	28.0 (27.2–28.8)	18.5 (17.9–19.1)	25.2 (24.4–26.0)	26.9 (26.1–27.7)	19.8 (19.1–20.5)	23.2 (22.2–23.9)
Chronic pulmonary disease	49.8 (48.7–50.9)	49.0 (48.0–50.0)	51.7 (50.6–52.8)	49.5 (48.4–50.6)	50.6 (49.5–51.7)	53.5 (52.4–54.6)	50.1 (49.0–51.2)	52.3 (51.2–53.4)	50.6 (49.5–51.7)	52.5 (51.4–53.6)	50.8 (49.7–51.9)
Dementia	5.9 (5.5–6.3)	4.4 (4.1–4.7)	1.6 (1.4–1.8)	2.3 (2.1–2.5)	5.5 (5.1–5.9)	3.9 (3.6–4.2)	3.5 (3.2–3.8)	2.5 (2.3–2.7)	6.3 (5.9–6.7)	2.6 (2.4–2.8)	4.6 (4.3–4.9)
EpiChron, Aragon, Spain (n = 211,284)											
Hypertension	51.2 (48.2–54.2)	43.4 (40.6–46.2)	37.7 (35.1–40.3)	37.4 (34.8–40.0)	51.3 (48.3–54.3)	48.6 (45.6–51.6)	41.5 (38.8–44.2)	39.1 (36.4–41.8)	55.2 (52.0–58.4)	41.7 (39.0–44.4)	44.3 (41.5–47.2)
Diabetes	15.2 (13.5–16.9)	11.9 (10.4–13.4)	11.3 (9.9–12.7)	9.4 (8.1–10.7)	14.4 (12.8–16.0)	14.3 (12.7–15.9)	11.7 (10.2–13.2)	9.3 (8.0–10.6)	15.9 (14.2–17.6)	11.2 (9.8–12.6)	12.2 (10.7–13.7)
Hyperlipidaemia	37.4 (34.8–40.0)	34.3 (31.8–36.8)	30.8 (28.4–33.2)	31.1 (28.7–33.5)	39.1 (36.4–41.8)	40.2 (37.5–42.9)	34.8 (32.3–37.3)	32.7 (30.3–35.1)	39.8 (37.1–42.5)	36.9 (34.3–39.5)	35.3 (32.8–37.9)
Obesity	21.2 (19.2–23.2)	19.8 (17.9–21.7)	32.1 (29.7–34.5)	19.1 (17.2–21.0)	21.8 (19.8–23.8)	25.3 (23.2–27.4)	21.0 (19.0–23.0)	21.0 (19.0–23.0)	18.2 (16.4–20.0)	22.5 (20.5–24.5)	21.6 (19.7–23.6)
History of cerebral arterial disease	5.4 (4.4–6.4)	4.3 (3.4–5.2)	2.3 (1.7–2.9)	2.4 (1.7–3.1)	5.2 (4.2–6.2)	4.1 (3.2–5.0)	3.0 (2.3–3.7)	3.3 (2.5–4.1)	5.3 (4.3–6.3)	3.1 (2.3–3.9)	3.9 (3.0–4.7)
History of ischaemic heart disease	4.6 (3.7–5.5)	3.7 (2.9–4.5)	2.3 (1.7–2.9)	2.7 (2.0–3.4)	5.2 (4.2–6.2)	3.9 (3.1–4.7)	2.7 (2.0–3.4)	2.5 (1.8–3.2)	5.5 (4.5–6.5)	3.3 (2.5–4.1)	3.6 (2.8–4.4)
Chronic pulmonary disease	9.4 (8.1–10.7)	8.6 (7.4–9.8)	8.8 (7.5–10.1)	7.8 (6.6–9.0)	9.6 (8.3–10.9)	9.8 (8.5–11.1)	7.9 (6.7–9.1)	8.3 (7.1–9.5)	10.7 (9.3–12.1)	9.2 (7.9–10.5)	9.0 (7.7–10.2)
Dementia	2.8 (2.1–3.5)	1.8 (1.2–2.4)	0.8 (0.4–1.2)	0.9 (0.5–1.3)	2.6 (1.9–3.3)	1.5 (1.0–2.0)	1.8 (1.2–2.4)	0.7 (0.3–1.1)	4.0 (3.1–4.9)	1.3 (0.8–1.8)	1.8 (1.2–2.3)
SIDIAP, Catalonia, Spain (n = 260,720)											
Hypertension	33.9 (31.7–36.1)	27.9 (25.9–29.9)	23.4 (21.5–25.3)	25.5 (23.6–27.4)	40.7 (38.3–43.1)	33.3 (31.1–35.5)	30.1 (28.0–32.2)	27.9 (25.9–29.9)	38.0 (35.6–40.4)	25.8 (23.9–27.7)	30.9 (28.8–33.0)
Diabetes	12.5 (11.1–13.9)	10.2 (9.0–11.4)	9.6 (8.4–10.8)	8.6 (7.5–9.7)	15.2 (13.7–16.7)	13.1 (11.7–14.5)	11.2 (9.9–12.5)	10.2 (9.0–11.4)	15.2 (13.7–16.7)	9.3 (8.1–10.5)	11.5 (10.2–12.8)
Hyperlipidaemia	31.3 (29.2–33.4)	26.2 (24.2–28.2)	25.6 (23.7–27.5)	26.3 (24.3–28.3)	35.5 (33.2–37.8)	34.2 (32.0–36.4)	31.7 (29.5–33.9)	29.5 (27.4–31.6)	34.7 (32.4–37.0)	29.1 (27.0–31.2)	30.1 (28.0–32.2)

(*continued on next page*)

Table 3 (*continued*)

	SSRIs,% (95% CI)					SNRIs,% (95% CI)		TCA,% (95% CI)	NASSA,% (95% CI)	Other,% (95% CI)	
	Citalopram	Escitalopram	Fluoxetine	Paroxetine	Sertraline	Duloxetine	Venlafaxine	Amitriptyline	Mirtazapine	Agomelatine	Overall
Obesity	18.6 (16.9–20.3)	14.8 (13.3–16.3)	24.2 (22.3–26.1)	15.7 (14.2–17.2)	20.2 (18.5–21.9)	20.6 (18.9–22.3)	19.5 (17.8–21.2)	18.7 (17.0–20.4)	16.0 (14.5–17.5)	18.0 (16.4–19.6)	18.4 (16.7–20.0)
History of cerebral arterial disease	5.0 (4.1–5.9)	4.1 (3.3–4.9)	2.2 (1.6–2.8)	2.7 (2.1–3.3)	5.8 (4.9–6.7)	4.1 (3.3–4.9)	3.9 (3.1–4.7)	3.5 (2.8–4.2)	6.4 (5.4–7.4)	3.0 (2.3–3.7)	4.1 (3.4–4.9)
Chronic pulmonary disease	13.0 (11.6–14.4)	11.5 (10.2–12.8)	11.4 (10.1–12.7)	11.5 (10.2–12.8)	14.1 (12.7–15.5)	12.7 (11.3–14.1)	12.3 (11.0–13.6)	12.3 (11.0–13.6)	15.4 (13.9–16.9)	11.6 (10.3–12.9)	12.6 (11.2–14.0)
Dementia	2.6 (2.0–3.2)	2.5 (1.9–3.1)	0.6 (0.3–0.9)	1.3 (0.9–1.7)	2.7 (2.1–3.3)	1.1 (0.7–1.5)	2.0 (1.5–2.5)	0.6 (0.3–0.9)	5.2 (4.3–6.1)	0.9 (0.5–1.3)	2.0 (1.5–2.6)
Sweden (n = 1,806,881)											
Hypertension	45.5 (44.5–46.5)	33.1 (32.3–33.9)	25.9 (25.2–26.6)	32.1 (31.3–32.9)	31.6 (30.8–32.4)	40.7 (39.8–41.6)	31.8 (31.0–32.6)	46.8 (45.8–47.8)	48.0 (47.0–49.0)	36.6 (35.7–37.5)	40.0 (39.1–40.9)
Diabetes	9.5 (9.1–9.9)	6.2 (5.8–6.6)	5.0 (4.7–5.3)	5.4 (5.1–5.7)	6.2 (5.8–6.6)	9.9 (9.4–10.4)	6.2 (5.8–6.6)	10.2 (9.7–10.7)	9.8 (9.3–10.3)	6.4 (6.0–6.8)	8.2 (7.8–8.6)
Hyperlipidaemia	22.2 (21.5–22.9)	14.6 (14.0–15.2)	9.8 (9.3–10.3)	13.5 (13.0–14.0)	14.5 (13.9–15.1)	19.9 (18.4–19.6)	14.1 (13.6–14.6)	23.4 (22.7–24.1)	23.3 (22.6–24.0)	14.2 (13.7–14.7)	18.9 (18.3–19.5)
Obesity	2.9 (2.7–3.1)	3.5 (3.2–3.8)	5.7 (5.4–6.0)	3.2 (2.9–3.5)	3.4 (3.1–3.7)	5.9 (5.5–6.3)	4.4 (4.1–4.7)	4.7 (4.4–5.0)	3.0 (2.7–3.3)	5.5 (5.2–5.8)	3.7 (3.4–4.0)
History of cerebral arterial disease	8.6 (8.2–9.0)	3.8 (3.5–4.1)	1.7 (1.5–1.9)	2.4 (2.2–2.6)	3.8 (3.5–4.1)	3.5 (3.2–3.8)	2.9 (2.7–3.1)	5.1 (4.8–5.4)	8.5 (8.1–8.9)	2.1 (1.9–2.3)	5.7 (5.3–6.0)
History of ischaemic heart disease	10.1 (9.6–10.6)	4.9 (4.6–5.2)	2.3 (2.1–2.5)	4.2 (3.9–4.5)	5.1 (4.8–5.4)	5.7 (5.4–6.0)	4.0 (3.7–4.3)	8.2 (7.8–8.6)	10.8 (10.3–11.3)	3.4 (3.1–3.7)	7.5 (7.1–7.9)
Chronic pulmonary disease	8.3 (7.9–8.7)	7.4 (7.0–7.8)	7.6 (7.2–8.0)	6.9 (6.5–7.3)	7.3 (6.9–7.7)	9.0 (8.6–9.4)	7.4 (7.0–7.8)	9.3 (8.9–9.7)	9.6 (9.1–10.1)	8.1 (7.7–8.5)	8.3 (7.9–8.7)
Dementia	4.2 (3.9–4.5)	1.7 (1.5–1.9)	0.3 (0.2–0.4)	0.6 (0.5–0.7)	1.4 (1.2–1.6)	0.9 (0.8–1.0)	1.0 (0.9–1.1)	0.7 (0.6–0.8)	5.2 (4.9–5.5)	0.4 (0.3–0.5)	2.6 (2.3–2.8)

CI = confidence interval, NASSA = noradrenaline and specific serotonergic antidepressant, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Except in Denmark where the cumulative incidence was lower (10 per 1000 population), amitriptyline had a similar cumulative incidence in all populations (ranging from 21 to 29 per 1000 population). The cumulative incidence for mirtazapine was the highest in Denmark, Germany (where it was the second most commonly used antidepressant), and Sweden (where it was the third). Finally, the use of agomelatine was low in all populations, with a cumulative incidence below 10 per 1000 population in all data sources.

3.3. Baseline comorbidities of antidepressant initiators

The most prevalent comorbidities at baseline (percentage and 95% confidence interval) in the study antidepressant initiators were hypertension, diabetes, hyperlipidaemia, and obesity (Table 3). The highest prevalence of hypertension was found among initiators of mirtazapine in Aragon (55%) and Catalonia (38%) (Spain) and Sweden (48%) and among initiators of amitriptyline in Denmark (38%). In Germany, the highest prevalence of hypertension was found equal among initiators of amitriptyline and mirtazapine (63%). A similar pattern, although with lower prevalence compared with hypertension, was observed for other comorbidities. Conversely, the percentage of patients with obesity at baseline was higher among fluoxetine initiators and lower for mirtazapine initiators.

3.4. Hospitalisations in the 12 months prior to start date among antidepressant initiators

The number of hospitalisations among initiators of study antidepressants during the 12 months before the study start varied among populations, although a common pattern emerged. Mirtazapine initiators were more frequently hospitalised compared with initiators of the remaining study antidepressants in Aragon and Catalonia, Spain, and Sweden (percentages of at least one hospitalisation were 23%, 17%, and 33%, respectively) (Table 4). Although initiators of amitriptyline had the highest proportion of patients who had been hospitalised in the previous year in Denmark (37% of patients had at least 1 hospitalisation), the proportion of patients with recent hospitalisations was also high for initiators of mirtazapine (33% of patients with at least 1 hospitalisation). Similarly, in Germany initiators of duloxetine and escitalopram (56% and 48% of patients with at least one hospitalisation, respectively) had the highest proportion of patients who had been hospitalised in the previous year, followed by initiators of mirtazapine (47% of patients with at least one hospitalisation).

3.5. Patterns of antidepressant use among initiators

The recent use of any antidepressant during the 12 months prior to the current treatment episode is presented in Fig. 1. In all populations, citalopram initiators were among the patients with the highest proportions of no antidepressant use in the 12 months prior to the current treatment episode. Amitriptyline had the highest proportion with no use in Aragon and Catalonia (Spain) and in Germany. Conversely, the two SNRIs (duloxetine and venlafaxine) and agomelatine were the antidepressants with the higher proportion of patients who used two or more antidepressants during the 12 months prior to the current treatment episode (Fig. 1). Among the five populations, the overall proportion of initiators with no previous use of other study antidepressants in the 12 months prior to the current treatment episode was highest in Spain, Germany, and Denmark and lowest in Sweden.

Patterns regarding duration of the first treatment episode of current use and percentage of all treatment episodes of current use with combined use of other antidepressants during the study period are presented in Table 5. For all study antidepressants, the duration of the first treatment episode of current use was slightly longer in Catalonia (Spain) (range, 4 months for amitriptyline to 10 months for venlafaxine) and shorter in Germany (range, 2 months for amitriptyline to 4 months for fluoxetine) than in the other populations. The median duration of the first index episode was longer for venlafaxine initiators and shorter for amitriptyline initiators in all populations except in Sweden. The highest percentage of patients in the five populations who were using combined antidepressants during their current treatment episode was found in initiators of agomelatine, followed by venlafaxine and duloxetine initiators (in Denmark, amitriptyline also had a high percentage of multiple use).

4. Discussion

In this study, we characterised more than 4.8 million initiators of 10 antidepressants in Spain, Germany, Denmark, and Sweden. Overall, citalopram was the most prescribed study antidepressant, followed by mirtazapine. Agomelatine (one of the most recent study antidepressants available on the market) and paroxetine, were the least commonly

Table 4
Number of hospitalisations among study antidepressant initiators of each of the study antidepressants during the 12 months before the cohort inclusion date, by data source.

	SSRIs					SNRIs		TCA	NASSA	Other
	Citalopram	Escitalopram	Fluoxetine	Paroxetine	Sertraline	Duloxetine	Venlafaxine	Amitriptyline	Mirtazapine	Agomelatine
Denmark										
0	70.2%	68.4%	78.6%	76.9%	76.2%	73.6%	76.5%	62.9%	67.2%	77.8%
1	17.6%	17.7%	14.3%	14.4%	15.2%	15.9%	14.8%	20.3%	18.0%	14.2%
2+	12.1%	13.8%	7.1%	8.7%	8.6%	10.5%	8.7%	16.8%	14.8%	8.0%
GePaRD										
0	60.4%	52.0%	68.1%	65.2%	56.9%	44.1%	55.3%	56.7%	52.9%	53.9%
1+	39.6%	48.0%	31.9%	34.8%	43.1%	55.9%	44.7%	43.3%	47.1%	46.1%
EpiChron, Aragon, Spain										
0	84.2%	85.7%	89.5%	88.9%	82.7%	84.9%	86.1%	89.8%	76.7%	86.5%
1	10.8%	10.1%	7.7%	8.3%	11.5%	10.6%	10.1%	7.9%	15.0%	9.8%
2+	5.0%	4.2%	2.8%	2.9%	5.8%	4.5%	3.9%	2.4%	8.3%	3.7%
SIDIAP, Catalonia, Spain										
0	88.4%	88.8%	90.9%	91.4%	87.3%	88.7%	88.7%	90.1%	83.1%	91.4%
1	8.7%	8.2%	7.3%	6.8%	9.4%	8.7%	8.8%	7.8%	11.7%	6.5%
2+	3.0%	3.0%	1.9%	1.8%	3.3%	2.7%	2.5%	2.1%	5.2%	2.1%
Sweden										
0	73.8%	75.9%	80.2%	80.0%	79.3%	71.8%	76.7%	75.2%	66.8%	73.3%
1	13.8%	12.8%	11.8%	11.6%	12.2%	14.8%	13%	13.4%	15.8%	13.6%
2+	12.4%	11.2%	8.0%	8.4%	8.5%	13.4%	10.3%	11.4%	17.5%	13.1%

NA = not applicable, NASSA = noradrenaline and specific serotonergic antidepressant, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

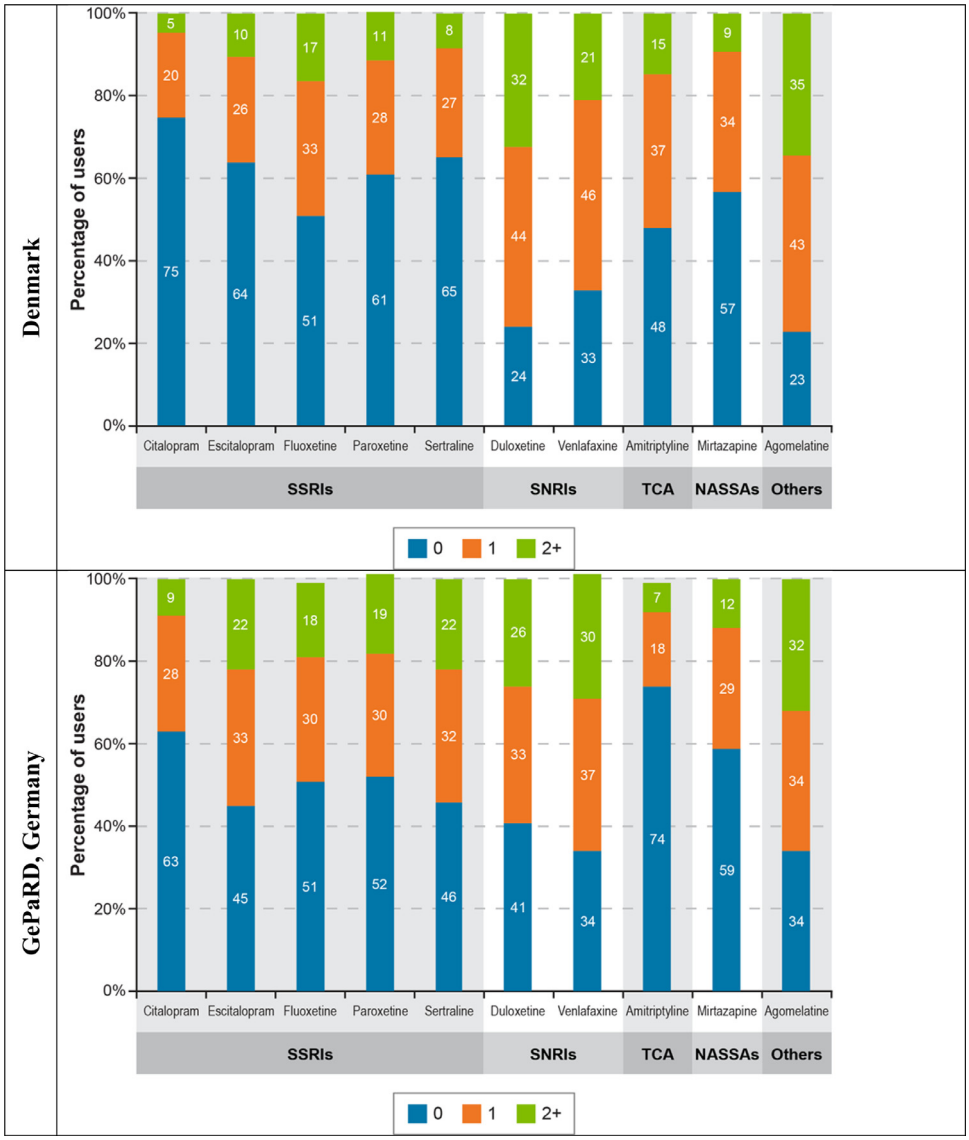

Fig. 1. Proportion of study antidepressants initiators by antidepressant treatment in the 12 months before drug initiation (no previous treatment, one antidepressant, two or more antidepressants) NASSA = noradrenaline and specific serotonergic antidepressant, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

prescribed antidepressants. Mirtazapine initiators were older compared to initiators of other antidepressants. Consequently, mirtazapine initiators had the highest percentage of comorbidities at baseline and also more hospitalisations in the 12 months prior to start date. Fluoxetine was the most common study antidepressant among younger and healthier initiators. Finally, citalopram and amitriptyline were the antidepressants with the lowest percentages of initiators who had used other antidepressant drugs in the 12 months prior to the current treatment episode, while agomelatine and SNRIs (duloxetine and venlafaxine) initiators had the highest percentage of antidepressants use in the year prior to the current treatment episode.

The results of the present study, which highlight citalopram as the most commonly prescribed among study antidepressant initiators in all populations but in Aragon (Spain), where escitalopram was the most often prescribed antidepressant, are in accordance with clinical guidelines to manage major depressive disorder in adults (Cipriani et al., 2018; National Institute for Health and Clinical Excellence, 2018b). The clinical guidelines for depression suggest using an SSRI (mostly citalopram, fluoxetine, and sertraline) as first-line treatment in adults (National Institute for Health and Clinical Excellence, 2018b). If clinical response is not adequate, the guidelines suggest a different SSRI agent or a newer generation antidepressant like mirtazapine, which was the second most prescribed antidepressant in Denmark, Germany, and Sweden. It was however unexpected that mirtazapine initiators in all populations but Sweden had a low percentage of prior use of other antidepressants in the 12 months prior to cohort inclusion, suggesting that mirtazapine may to some extent be used as a first-line agent in the studied populations. The faster onset of action and the more sedative effect of mirtazapine compared with SSRIs in the acute phase of depression might explain these results (Watanabe et al., 2011). Reimbursement policies vary by antidepressant in each of the participating countries, and this could potentially explain the observed variability in patterns of use of antidepressants. As an example, the study revealed differences in prescriptions in the two Spanish populations, with escitalopram being more frequently prescribed in Aragon, while citalopram was the number one option in Catalonia.

Overall, more than 50% of the antidepressant initiators receiving SSRIs (mostly citalopram and sertraline) had no prior use of other antidepressants, and a very low proportion of these patients used two or more antidepressants in the 12 months prior to current treatment

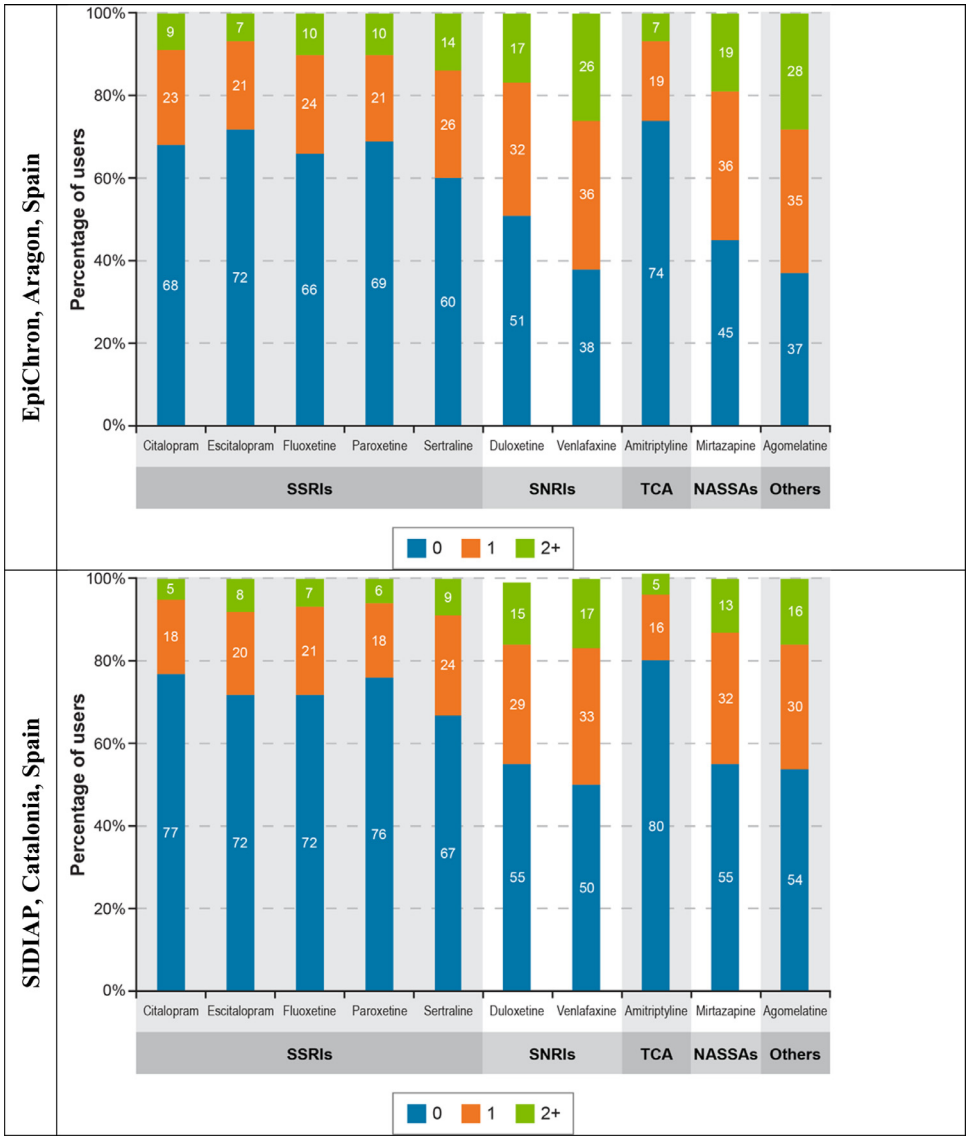

Fig. 1. (*continued*)

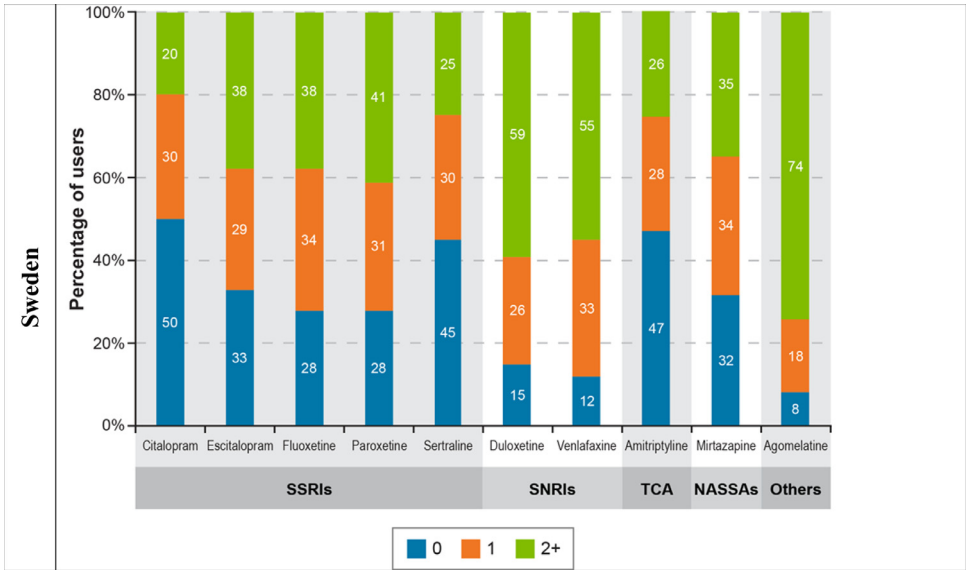

Fig. 1. (*continued*)

Table 5
Duration of treatment and multiple use of study antidepressants, by study population.

	SSRIs					SNRIs		TCA	NASSA	Others
	Citalopram	Escitalopram	Fluoxetine	Paroxetine	Sertraline	Duloxetine	Venlafaxine	Amitriptyline	Mirtazapine	Agomelatine
Denmark										
Duration (months) of first treatment episode in current use, median (IQR)	7.0 (4.6–15.4)	5.6 (2.5–12.9)	6.5 (5.1–13.5)	5.8 (3.9–13.0)	6.7 (5.4–13.9)	6.5 (2.5–16.3)	8.2 (5.2–18.7)	3.5 (3.5–5.9)	4.8 (2.6–9.4)	5.6 (2.5–13.1)
Percentage of all treatment episodes (current use) with combined use of other antidepressant, median (IQR)	0 (0–30.0)	9.5 (0–62.6)	9.2 (0–60.7)	0 (0–46.7)	0 (0–42.5)	34.8 (1.2–99.4)	22.0 (0–77.6)	40.8 (0–100.0)	16.3 (0–100.0)	69.2 (7.7–100.0)
GePaRD										
Duration (months) of first treatment episode in current use, median (IQR)	3.0 (2.0–6.1)	3.0 (2.0–7.1)	3.9 (2.1–7.2)	3.0 (2.0–6.2)	3.5 (2.0–7.9)	2.3 (1.8–5.0)	3.2 (1.9–7.4)	1.8 (1.5–2.4)	2.1 (1.6–3.1)	2.7 (2.2–5.6)
Percentage of all treatment episodes (current use) with combined use of other antidepressant, median (IQR)	0.0 (0.0–51.0)	18.6 (0.0–81.9)	1.7 (0.0–62.8)	2.8 (0.0–70.5)	11.0 (0.0–78.2)	9.3 (0.0–86.7)	26.4 (0.0–94.5)	0.0 (0.0–0.0)	0.0 (0.0–82.0)	44.0 (0.0–100.0)
EpiChron, Aragon, Spain										
Duration (Months) of first treatment episode in current use, median (IQR)	3.3 (2.2–7.9)	3.4 (2.2–7.9)	3.5 (2.2–7.7)	3.2 (2.2–7.3)	3.5 (2.3–8.3)	3.6 (2.2–9.8)	4.0 (2.3–10.3)	3.3 (2.1–5.1)	3.3 (2.3–7.3)	3.3 (2.2–7.7)
Percentage of all treatment episodes (current use) with combined use of other antidepressant, median (IQR)	0 (0–14.2)	0 (0–6.9)	0 (0–10.7)	0 (0–10.7)	0 (0–22.5)	0 (0–33.5)	5.1 (0–50.8)	0 (0–1.4)	5.3 (0–67.8)	25.0 (0–74.5)
SIDIAP, Catalonia, Spain										
Duration (months) of first treatment episode in current use, median (IQR)	7.6 (3.2–17.5)	8.4 (3.2–19.6)	7.3 (3.3–16.9)	7.3 (3.0–15.9)	7.3 (3.0–16.3)	8.2 (3.2–19.8)	9.7 (3.5–22.2)	3.7 (2.1–9.5)	6.3 (2.4–15.0)	8.0 (3.3–18.8)
Percentage of all treatment episodes (current use) with combined use of other antidepressant, median (IQR)	0.0 (0.0–10.0)	0.0 (0.0–19.9)	0.0 (0.0–15.6)	0.0 (0.0–10.6)	0.0 (0.0–19.4)	3.9 (0.0–49.3)	9.3 (0.0–63.1)	0.0 (0.0–0.0)	8.3 (0.0–100.0)	18.8 (0.0–100.0)
Sweden										
Duration (months) of first treatment episode in current use, median (IQR)	4.6 (2.6–10.3)	3.3 (2.1–7.2)	4.5 (2.3–7.7)	4.6 (2.1–7.9)	4.6 (2.3–8.8)	2.2 (1.7–4.5)	2.8 (1.6–4.7)	4.6 (2.6–5.9)	3.2 (2.1–5.7)	2.2 (1.4–4.1)
Percentage of all treatment episodes (current use) with combined use of other antidepressant, median (IQR)	0 (0–14.5)	0 (0–50.2)	0 (0–42.6)	0 (0–39.1)	0 (0–25.0)	17.4 (0–77.2)	19.2 (0–72.9)	0 (0–14.8)	15 (0–95.9)	69.2 (0–100.0)

CI = confidence interval, IQR = interquartile range, NA = not applicable, NASSA = noradrenaline and specific serotonergic antidepressant, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

episode, except in Sweden. Also, most SSRI initiators in the five populations did not have combined use with other antidepressants during the current treatment episode. Both results suggest that, in general, citalopram and to a minor degree sertraline, escitalopram, paroxetine, and fluoxetine were mostly used as first-line treatment and used in monotherapy. On the other hand, the two SNRIs included in the study, duloxetine and venlafaxine, as well as agomelatine were seemingly mostly used as second-line treatment, in agreement with clinical guidelines for major depression (National Institute for Health and Clinical Excellence, 2018b). This interpretation is also supported by the high proportion of patients who used two or more antidepressants in the 12 months prior to start date as well as by the high percentage of patients who used other antidepressants concomitantly during the study period. However, of the antidepressants included in this study, duloxetine, venlafaxine, and agomelatine are the ones introduced in the European Union market more recently, which could explain these results.

The main results discussed in the present study are focused on management of depression, but all the study antidepressants are also used in other conditions, which may explain some of the results observed in the present study. For example, the TCA amitriptyline was mainly used as monotherapy, and use of other antidepressants in the 12 months prior to the current treatment episode was uncommon. Amitriptyline is recommended as first-line treatment in the management of neuropathic pain (Fornasari, 2017; National Institute for Health and Clinical Excellence, 2018a) and can also be used in the context of migraine, stress, and sleep disorders (Aarts et al., 2016; Moore et al., 2012, 2015). For these indications, amitriptyline can be used as monotherapy, which accords with the observations from Germany, Sweden, and Spain, or in combination with pregabalin/gabapentin, opioids, or SNRIs (Holbech et al., 2017). Finally, the two SNRIs in the study, duloxetine and venlafaxine, as well as the SSRIs are approved treatments for anxiety disorders (Aarts et al., 2016).

The present study revealed that initiators of study antidepressants frequently had several comorbidities, hypertension being the most frequent. Mirtazapine was the most prescribed antidepressant among patients with a higher percentage of comorbidities at baseline, which is probably related to the fact that mirtazapine initiators were the oldest initiators in all populations (median age range, 54–67 years). The unique adverse event profile of mirtazapine including sedation and increase in appetite may justify its use in older patients compared with other antidepressants (Watanabe et al., 2011). It is important to note that mirtazapine and amitriptyline, particularly in the Nordic countries, were the most commonly prescribed antidepressants among patients presenting comorbidities such as hypertension, diabetes, or hyperlipidaemia, which does not reflect the clinical guidelines that recommend the use of citalopram or sertraline in these patient groups (National Institute for Health and Clinical Excellence, 2018b) which may be partly explained for the approved use in other conditions. Conversely, fluoxetine initiators were younger compared to mirtazapine initiators and had the lowest percentage of comorbidities at baseline among all study antidepressants. These results are likely associated with the high efficacy of fluoxetine in reducing depressive symptoms in children and adolescents (Cipriani et al., 2016). For obesity, the percentage was higher among fluoxetine initiators and lower among mirtazapine initiators, which is in accordance with previous evidence that relates mirtazapine to a greater risk of weight gain and fluoxetine with weight loss (Gafoor et al., 2018). Because we were not able to differentiate whether differences in prevalence of comorbidities between countries reflected an actual variation or differences in the type of data available in each population, this could not be further interpreted.

5. Limitations

The results of the present study should be interpreted in the context of its limitations. First, although the data sources provide detailed information on filled prescriptions, which can be considered complete, this information may not reflect actual use. However, information on dispensing more closely reflects actual use by the patients than information obtained by prescribing data (Pottegard et al., 2014). Second, the present study used a new-user design and then focused on initiators of each of the study antidepressants only. Therefore, prevalent users have not been evaluated. Third, the lack of information on the indication of medications in the present study hampered the possibility of studying the differences in the indications across the different study antidepressants and data sources. For this reason, discussion on the present study focuses on depression and not on other conditions that can be treated with the study antidepressants. Fourth, only a selected group of antidepressants have been included in the present study, based on the list of antidepressants included in the Agomelatine PASS (Pladevall, 2018), and therefore the results of this study did not include all available antidepressants in the ATC N06A group. Finally, the heterogeneity of health care systems and of the type of data across data sources needs to be considered when evaluating comorbidities associated with the different antidepressants. Information recorded in SIDIAP (Catalonia, Spain) and EpiChron (Aragon, Spain) data sources is based on primary care and hospital discharge electronic medical records, information recorded in the GePaRD (Germany) data source is based on insurance claims from ambulatory care visits and hospitalisations, and information in Denmark and Sweden registers is based on hospital diagnoses only.

On the other hand, the present study has a number of strengths. The present study presented data from 2009 to 2014, the most recent period reported in the literature. In addition, it is one of the largest drug utilization studies on the use of antidepressants in Europe, including almost 5 million initiators in Spain, Germany, Denmark, and Sweden covering a base population of more than 36 million people. Also, we have studied a number of important comorbidities at baseline. Finally, we have well-defined populations with prospectively collected data.

6. Conclusions

Results of this study conducted in Denmark, Germany, Spain, and Sweden including 4.8 million initiators of study antidepressants suggest that citalopram and mirtazapine are the most commonly used antidepressants, followed by other SSRIs (sertraline, escitalopram, paroxetine, and fluoxetine). Mirtazapine was the second most used antidepressant in most of the populations. Agomelatine, which is commonly used as second-line treatment, and paroxetine were the least used antidepressants in the participating populations. Mirtazapine was the antidepressant most commonly prescribed among older study antidepressant initiators and was the one with the highest percentage of comorbidities in patients at baseline and with the highest number of hospitalisations. Fluoxetine was commonly prescribed among young patients with a low percentage of comorbidities at baseline.

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Author contributions

Authors J.F., M.P., E.J., N.D., and S.P. planned the study. A.P., T.R., B.P., R.M., L.B., M.C., M.H., T.S., A.P.T., M.G., D.H., J.H., and J.C. undertook the statistical analysis of the different data sources. J.F., M.P., S.P. and J.R. completed the interpretation of the results with contributions from all authors. J.F., M.C., M.P., S.P. and J.R. wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Supplementary materials

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