Sex Differences in Antidepressant Acceptability According to Filled Prescription Sequences in a Nationwide Cohort Study

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Abstract

Objective: The prevalence of depressive and anxiety disorders is higher in women than in men. In contrast, there is still no clear consensus on the existence of sex-related differences in the effectiveness of antidepressant treatments for these disorders. This real-world study used filled prescription sequences to compare antidepressant medications between women and men at a medication level according to their acceptability (ie, combination of efficacy and tolerability).

Methods: In a nationwide cohort from the French national health data system (Système National des Données de Santé [SNDS]), 1.2 million people were identified as new antidepressant users for any condition in 2011. The outcome was clinical acceptability as measured by the continuation/change ratio over the 6-month period following the introduction of the first-line treatment. Continuation was defined as at least 2 refills of the same treatment. Change was defined as at least one filled prescription of another antidepressant, an antipsychotic medication, or a mood stabilizer. Adjusted odds ratios (aORs) were computed through multivariable binary logistic regressions.

Results: Overall, after the first prescription of an antidepressant, the continuation/change ratio was slightly higher for women than men (aOR [95% CI], 1.06 [1.05–1.08]), with escitalopram ranking first in both. Sex-by-medication interactions were significant for paroxetine (0.91 [0.88–0.95]) and fluoxetine (1.19 [1.12–1.26]) only. Specifically, fluoxetine was significantly more acceptable in female than in male participants (0.73 [0.70–0.75] vs 0.63 [0.60–0.67]), whereas paroxetine was more acceptable in male than in female participants (0.75 [0.72–0.78] vs 0.68 [0.66–0.70]).

Conclusion: These real-world data may help practitioners and policymakers prioritize choice of antidepressant medications in women and men.

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Major depressive disorder (MDD) and anxiety disorders are both major public health issues given their high lifetime prevalence and significant contributions to individual suffering, disability, medical morbidity, and mortality risk.[1–5] Antidepressant medications are recommended as first-line pharmacological treatments for several anxiety disorders as well as for moderate to severe MDD episodes.[6–8] Thus, they are one of the most commonly prescribed medication classes worldwide.[9,10] Selective serotonin reuptake inhibitors (SSRIs) are widely recommended as the first-line class, with no specific SSRI standing out according to the literature.[11–15] Response to first-line antidepressant medications (ie, a reduction of at least 50% of the intensity of symptoms) is observed in about 50% of patients with MDD in real-life settings, and less than 1 out of 3 patients achieve symptom remission.[16,17] Variations in treatment response may reflect the clinical heterogeneity of patients with depression. Increased emphasis on precision medicine has intensified interest in identifying whether some antidepressants are associated with better response than others in specific subgroups of patients.

Clinical Points

- The prevalence of depressive and anxiety disorders is higher in women than in men. In contrast, there is still no clear consensus on the existence of sex-related differences in the effectiveness of antidepressant treatments for these disorders.
- Although escitalopram has the highest acceptability in both women and men, the present study provides evidence of sex differences in antidepressant acceptability for 2 medications, with fluoxetine being more acceptable for women than for men and the reverse being observed for paroxetine, suggesting that weight-related concerns may be important in personalizing antidepressant treatment.

When it comes to patient characteristics associated with the risk of anxiety disorders or MDD, sex is an obvious candidate. The prevalence of MDD in women is nearly double that in men, and most anxiety disorders are also more prevalent in women than in men.[18,19] Regarding MDD, women as compared to men show greater severity, weight gain, anxiety, physical manifestations, earlier age of onset, and increased duration of depressive episodes.[20–22] Several hypotheses have been put forward to account for these differences between men and women, including both biological (eg, the role of sex-related hormones) and psychosocial factors (eg, the role of societally constructed characteristics of men and women), with possible interplay between these factors.[23]

In contrast, there is still no clear consensus on whether there are sex-related differences in the effectiveness of antidepressant treatments. Several studies have shown that women responded better to antidepressants than men,[24–27] others found the reverse,[28,29] and still others have found no difference.[30–33] One hypothesis to account for such heterogeneous findings is that the acceptability of individual antidepressants may vary by sex. Since these differences may occur at an individual medication level (ie, specific medications like escitalopram or venlafaxine), considering each antidepressant medication individually is warranted to evaluate this possibility.

In light of the number of available antidepressant medications, a randomized controlled trial (RCT) addressing this issue could not be sufficiently powered, and network meta-analyses would share the low generalizability of RCTs.[34,35] Administrative claims databases, which capture large-scale data from routine clinical settings, may offer unique opportunities to address these issues.[36]

After a first prescription of an antidepressant, the decision to refill the same prescription or to prescribe another medication reflects a clinical appraisal of the acceptability of the first prescription, which encompasses both efficacy and tolerability. In a proof-of-concept study, we showed that patients who followed a sequence consistent with a continuation of the first prescribed treatment—suggesting both efficacy and tolerability—had a lower level of depressive symptoms than those who followed a sequence including a change of the original treatment (either medication switch or combination).[37] This result validates the use of sequences of filled antidepressant prescriptions to rank antidepressants according to their relative clinical acceptability.[38,39]

Based on the French national health data system (Système National des Données de Santé [SNDS]) database, we used filled prescription sequences to compare the acceptability of individual antidepressant medications in women and men.

METHODS

About the SNDS

The SNDS collects individual characteristics of French residents who are beneficiaries of the various national health insurance schemes. Individual characteristics include age, sex, commune of residence (ie, the smallest administrative unit, approximately 36,000 across France), vital status (date of death), and eligibility for complementary health insurance coverage (CMU-C, for individuals aged <60 years), which is attributed to people or households with low annual income.[40] A social deprivation index (higher meaning more deprived) is also available at the scale of the commune, based on data regarding household income, education level, occupational grade, and unemployment rate.[41] All filled prescriptions and procedures, which are performed on an outpatient basis or in health care institutions and funded or reimbursed by the national health insurance, are recorded. Algorithms allow identifying 58 nonexclusive groups of health conditions (diseases, episodes of care, and chronic treatments) using the *ICD-10* codes for long-term diseases (offering 100% reimbursement of health care) or hospitalizations, medications, or medical procedures.[42,43] In France, there is no insurance or cost restriction regarding the antidepressant medications used in this analysis, which limits selection biases based on socioeconomic status.

Study Population

New users of antidepressants were included at the date of their first filled prescription of an antidepressant from January 1, 2011, to December 31, 2011. New antidepressant use was defined by the absence of prescriptions for any psychotropic drugs in 2009 and 2010, except benzodiazepines and Z-drugs, together with no prior psychiatric diagnosis identified in the past 4 or 5 years (depending on the date of the first-filled

prescription). Patients were followed for a rolling year starting on the day of the first-filled antidepressant prescription. Then, people aged less than 18 years were excluded.

Antidepressants were identified in the SNDS by anatomical therapeutic chemical (ATC) codes starting with "N06A." Since duloxetine (ATC code N06AX21) is frequently used in the treatment of neuropathic pain or fibromyalgia, it was excluded from the analysis. Likewise, filled prescriptions of less than 1,500 mg per prescription (ie, presumably less than 50 mg per day, under the assumption of a prescription for at least 1 month) for amitriptyline (ATC code N06AA09) were excluded from our analyses, since low dosage amitriptyline is frequently used as an analgesic rather than an antidepressant.[44]

Primary Outcome

The primary endpoint was clinical acceptability as measured by the continuation/change ratio for each medication. Continuation sequence was defined as at least 2 refills of the same antidepressant with no delivery of a different antidepressant, an antipsychotic medication, or a mood stabilizer over the 6-month period following the first prescription[37] (ie, a total of 3 filled prescriptions). Change sequence was defined as at least 1 delivery of either a different antidepressant, an antipsychotic medication, or a mood stabilizer over the 6-month period following the first prescription (Supplementary Figure 1). Sequences without any refill or only 1 refill of the first prescribed antidepressant over the 6-month period were labeled as "early termination" sequences and considered of uncertain meaning.[37] For instance, patients with only 1 filled prescription may not have been reevaluated or may have been reevaluated as no longer needing an antidepressant medication. Therefore, the primary outcome for each patient was a binary variable with 2 categories: continuation or change. The continuation/change ratio was computed for each antidepressant medication.

Covariates

The following covariates were considered: age, social deprivation index, benefit from CMU-C, the presence of ≥1 chronic nonpsychiatric disease, specialty of the physician who prescribed the first antidepressant classified into 3 categories (General Practitioners (GPs) and hospital practitioners (including hospital-based psychiatrists), psychiatrists with private practice and other specialists with private practice), and benzodiazepines or Z-drugs filled prescriptions (ie, participants having ≥3 filled prescriptions during the year of inclusion).

Statistical Analysis

All 95% CIs were calculated using nonparametric bootstrap sampling with percentile intervals.

We first ranked individual antidepressant medications according to their clinical acceptability while stratifying by sex. Multivariable binary logistic regression models were used to calculate adjusted odds ratios (aORs).

To further examine whether the associations between antidepressant treatments and acceptability differed by sex, we then searched for interactions between sex and each antidepressant individually (ie, a given molecule vs all the other molecules), while keeping sex and the molecule in the model. We used Bonferroni-corrected *P* value of .05/21 (ie, .0024) to account for multiple testing.

Due to missing data for those living in overseas territories and aged more than 60, respectively, social deprivation index and CMU-C were only used for descriptive or sensitivity analyses.

SAS Enterprise software version 7.13 (SAS Institute Inc) was used to create variables and extract data. All analyses were performed using R software, version 4.1.3.

The Caisse Nationale d'Assurance Maladie, as a health research institute, has permanent access to the SNDS database approved by decree and the French data protection authority (Commission Nationale de l'Informatique et des Libertés). Although the data analyzed in the present study came from human participants, retrospective research on health care data does not warrant individual written consent or institutional review board approval by French law.

RESULTS

Participants

In 2011, nearly 1.2 million people were defined as new antidepressant users. After applying the eligibility criteria, the population included 847,922 participants. Not considering sequence of uncertain meaning (early termination), the study population included 382,275 patients (Supplementary Figure 1).

The characteristics of the study population are displayed in Table 1. There were 257,597 female and 124,678 male participants (Supplementary Figure 1). Compared to women, men tended to have a first prescription more often by a psychiatrist (9.4% vs 7.4%), were more likely to have at least 1 nonpsychiatric comorbid condition (27.8% vs 21.3%), and were less likely to fill a coprescription of benzodiazepines (32.8% vs 37.7%).

In both men and women, compared to participants with a change sequence, those who continued the same antidepressant were more likely to be older, have at least 1 chronic nonpsychiatric disease, have a general or hospital practitioner as their first prescriber, and have a lower social deprivation index and were less likely to benefit from CMU-C and have at least 3 filled prescriptions of benzodiazepines and Z-drugs (Table 2).

Table 1.
Characteristics of the Study Population

	N	Female participants N = 257,597 %	Male participants N = 124,678 %	*P* value
Age				
<30 y	40,263	10.6	10.3	<.001
30–39 y	67,225	17.6	17.5	
40–49 y	82,116	21.3	21.8	
50–59 y	70,155	17.8	19.5	
60–69 y	43,023	11.2	11.5	
≥70 y	79,493	21.5	19.4	
Deprivation index (quintiles) (N = 354,702)				
1 less deprived	66,369	19.0	19.8	<.001
2	69,417	19.5	19.8	
3	71,810	20.3	20.2	
4	70,100	20.0	19.3	
5 more deprived	70,848	20.0	19.8	
Overseas territories	4,158	1.2	1.1	
CMU-C (if <60 y) (N = 283,263)	26,410	7.1	6.7	<.001
First prescriber				
GP and hospital practitioner	336,656	88.9	86.1	<.001
Psychiatrist	30,637	7.4	9.4	
Another specialist	14,982	3.6	4.6	
At least 1 chronic disease[a]	89,021	21.3	27.8	<.001
Drugs reimbursed[b]				
Z-drugs	63,957	16.8	16.6	.08
Benzodiazepines	137,901	37.7	32.8	<.001

[a]In the SNDS, algorithms identify 48 nonexclusive groups of chronic nonpsychiatric diseases.
[b]At least 3 filled prescriptions in the year of inclusion.
Abbreviations: CMU-C = complementary health insurance coverage, GP = general practitioner.

Ranking Antidepressants in Women and Male Participants

Regardless of individual antidepressant medications, the continuation/change ratio was slightly higher for women than for men in a fully adjusted model before stratification by sex (aOR [95% CI], 1.06 [1.05–1.08]).

We ranked antidepressant medications with at least 100 observed sequences according to the continuation/change ratio, adjusting for the described covariates (Table 3). In women participants, escitalopram ranked first, followed by fluoxetine, paroxetine, sertraline, citalopram, and venlafaxine.

Among male participants, the ranking was mostly the same, with only fluoxetine falling behind paroxetine and sertraline (Table 3; Figure 1).

Interaction With Sex

Results from models including a sex-by–antidepressant medication interaction are displayed in Table 3. There were significant interactions for 4 molecules out of 21, including 2 positive interactions, for fluoxetine and escitalopram, and 2 negative interactions, for paroxetine and clomipramine (Table 3). However, only the interactions with paroxetine (aOR for interaction [95% CI], 0.91 [0.88–0.95]) and fluoxetine (aOR for interaction [95% CI], 1.19 [1.12–1.26]) remained significant after applying a Bonferroni correction for multiple testing. Specifically, fluoxetine was significantly more acceptable in female than in male participants (aOR [95% CI], 0.73 [0.70–0.75] vs 0.63 [0.60–0.67]) whereas paroxetine was more acceptable in male than in female participants (aOR [95% CI], 0.75 [0.72–0.78] vs 0.68 [0.66–0.70]) (Table 3).

Sensitivity Analyses

For all rankings, sensitivity analyses including social deprivation index and CMU-C (only in patients younger than 60 years for this covariate) resulted in smaller samples but yielded similar results (data available on request).

Post hoc Analysis

We observed significant differences in the acceptability of antidepressant medications between men and women. To further investigate this finding, we conducted post hoc analyses comparing the number of filled prescriptions for each medication in both sexes. These additional analyses aimed to provide deeper insights into the observed sex-related differences in treatment acceptability.

Table 2.
Sequences of Prescriptions According to the Characteristics of the Population

	Women				Men			
	N	% Continuation	% Change	OR (95%CI)[a]	N	% Continuation	% Change	OR (95%CI)[a]
Total	257,597	76.0	24.0		124,678	75.0	25.0	
Age								
<30 y	27,376	68.7	31.3	Ref	12,887	70.0	30.0	Ref
30–39 y	45,349	72.0	28.0	1.17 (1.13–1.21)	21,876	71.4	28.6	1.07 (1.02–1.12)
40–49 y	54,921	74.2	25.8	1.31 (1.27–1.35)	27,195	13.6	26.4	1.19 (1.14–1.25)
50–59 y	45,868	76.3	23.7	1.47 (1.42–1.52)	24,287	74.8	25.2	1.28 (1.22–1.34)
60–69 y	28,732	80.3	19.7	1.86 (1.79–1.93)	14,291	79.0	21.0	1.62 (1.53–1.71)
≥70 y	55,351	80.8	19.2	1.91 (1.85–1.98)	24,142	79.7	20.3	1.69 (1.61–1.77)
Deprivation index (quintiles) (N = 354,702)								
1 less deprived	45,747	76.8	23.2	Ref	22,622	76.6	23.4	Ref
2	46,859	77.0	23.0	1.01 (0.98–1.04)	22,558	76.3	23.7	0.98 (0.94–1.02)
3	48,791	76.1	23.9	0.96 (0.93–0.99)	23,019	75.5	24.5	0.94 (0.90–0.98)
4	48,039	76.5	23.5	0.98 (0.95–1.01)	22,061	75.6	24.4	0.95 (0.91–0.99)
5 more deprived	48,230	74.2	25.8	0.87 (0.84–0.89)	22,618	73.7	26.3	0.85 (0.82–0.89)
CMU-C (N = 283,263)	18,144	67.4	32.6	0.64 (0.62–0.66)	8,266	70.5	29.5	0.78 (0.74–0.82)
First prescriber								
GP	229,319	76.2	23–8	Ref	107,337	75.3	24.7	Ref
Psychiatrist	918,977	70.7	29.3	0.76 (0.73–0.78)	11,660	70.2	29.8	0.77 (0.74–0.81)
Another specialist	9,301	75.1	24.9	0.94 (0.90–0.99)	5,681	77.5	22.5	1.13 (1.06–1.20)
At least 1 chronic disease[b]	54,338	78.9	21.1	1.26 (1.23–1.29)	34,683	78.9	21.1	1.36 (1.23–1.40)
Drugs reimbursed[c]								
Z-drugs	43,317	73.7	26.3	0.88 (0.86–0.90)	20,640	72.7	27.3	0.87 (0.84–0.90)
Benzodiazepines	96,993	73.1	26.9	0.80 (0.78–0.81)	40,908	72.3	27.7	0.82 (0.80–0.84)

[a]OR and 95% CI are those of continuation over change, unadjusted.
[b]In the SNDS, algorithms identify 48 nonexclusive groups of chronic nonpsychiatric diseases.
[c]At least 3 filled prescriptions in the year of inclusion.
Abbreviations: CMU-C = complementary health insurance coverage, GP = general practitioner, OR = odds ratio.

The paroxetine prescription rate was lower in women (15.9%) than in men (17.6%), while the fluoxetine prescription rate was higher in women (8.9%) than in men (7.3%). Escitalopram, the most commonly prescribed antidepressant, also had a higher prescription rate in women (39.0%) than in men (37.6%). The prescription rates for other commonly prescribed antidepressants showed little variation between men and women (Supplementary Figure 2). The observed differences were statistically significant using the χ^2 test ($P < .0001$).

DISCUSSION

Summary of Results

This nationwide study used filled prescription sequences to examine sex differences in the acceptability of antidepressants at a medication level. From a source population of over 1 million new antidepressant users, the first-line antidepressant acceptability was only slightly higher for women than for men, with no significant sex differences regarding most antidepressants and escitalopram ranking first in both cases. However, significant sex differences were identified regarding 2 drugs accounting for more than 20% of the market: fluoxetine was more acceptable in women than in men, whereas paroxetine was more acceptable in men than in women. These results suggest that while sex may not be a key feature in the personalization of several antidepressant medications, clinicians may pay attention to sex differences regarding these 2 specific medications. Specifically, fluoxetine ranked second among women while paroxetine ranked second among men.

Strengths and Limitations

Study strengths include the large sample size, the length of follow-up, the representativeness of the population, and the generalizability of the results. Our ability to detect rather small effect sizes regarding 2 of 21 medications suggests that the study was adequately powered enough to detect sex differences, despite significance threshold corrections for multiple testing. Regarding external validity, a previous study replicated the ranking of the proof-of-concept study using the same methods but on a nationwide French cohort, thus providing evidence that filled prescription sequences is a widely available, robust, and reproducible tool to rank the acceptability of antidepressant medications in real-life settings.[39]

Some limitations must be acknowledged. First, our study is observational, which raises concerns about

Table 3.

Frequency of Continuation and Interactions Between Sex (Female vs Male) and Medications

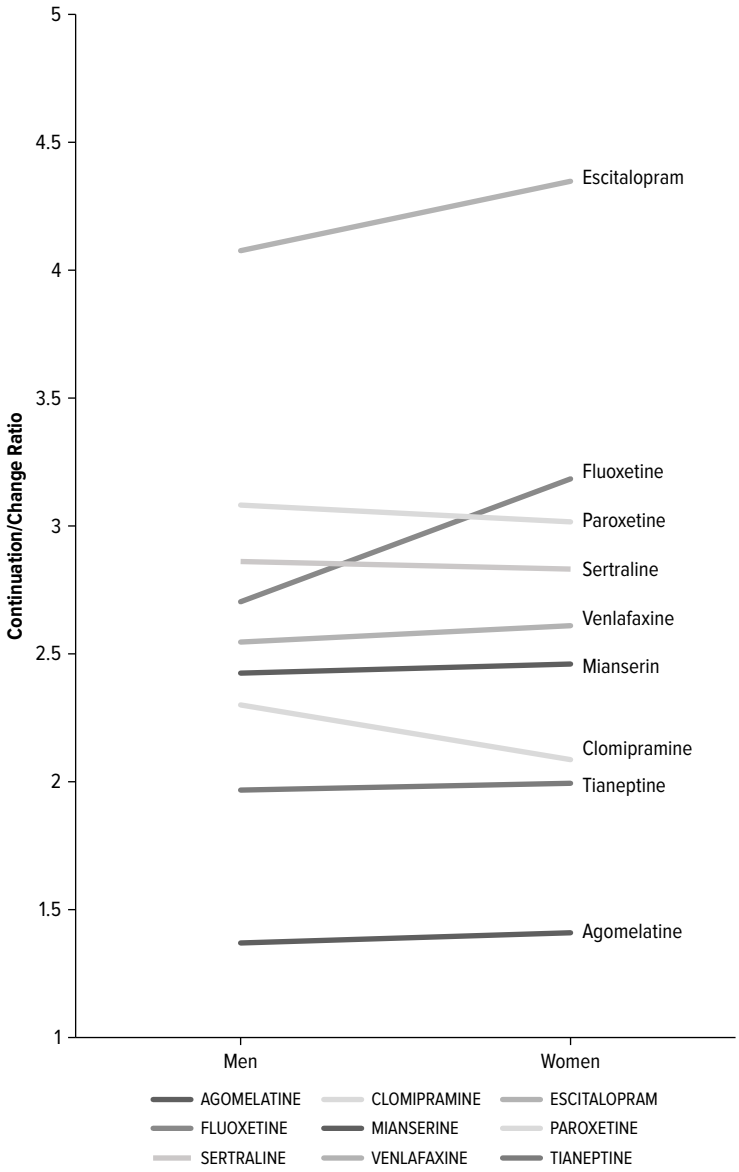
	Female			Male			Interaction
	N	% Continuation	aOR (95% CI)[a]	N	% Continuation	aOR (95% CI)[a]	aOR (95% CI)[b,c]
Agomelatine	3,088	58.5	0.34 (0.32–0.37)	1,681	57.8	0.35 (0.32–0.39)	0.99 (0.87–1.11)
Amitriptyline	2,908	67.6	0.45 (0.42–0.49)	1,811	68.9	0.52 (0.47–0.58)	0.89 (0.78–1.01)
Amoxapine	42	57.1	0.28 (0.15–0.52)	27	55.6	0.25 (0.12–0.55)	NR[d]
Citalopram	17,551	74.6	0.64 (0.62–0.66)	8,190	72.8	0.63 (0.60–0.66)	1.05 (0.99–1.12)
Clomipramine	2,154	67.6	0.45 (0.41–0.49)	1,550	69.7	0.56 (0.50–0.62)	0.92 (0.71–0.95)
Dosulepine	718	66.9	0.45 (0.38–0.52)	331	60.1	0.38 (0.30–0.47)	1.23 (0.94–1.61)
Doxepin	193	71.0	0.53 (0.39–0.73)	111	69.4	0.52 (0.35–0.80)	1.02 (0.61–1.71)
Escitalopram	100,433	81.3	Ref	4,632	80.3	Ref	1.04 (1.01–1.08)
Fluoxetine	23,029	76.1	0.73 (0.70–0.75)	9,109	73.0	0.63 (0.60–0.67)	**1.19 (1.12–1.26)**
Fluvoxamine	270	67.0	0.46 (0.36–0.59)	227	66.1	0.47 (0.36–0.62)	1.00 (0.68–1.45)
Imipramine	166	65.7	0.40 (0.29–0.55)	109	56.9	0.29 (0.20–0.43)	1.37 (0.83–2.26)
Maprotiline	229	66.8	0.42 (0.32–0.55)	82	63.4	0.39 (0.25–0.61)	1.12 (0.66–1.90)
Mianserin	11,881	71.1	0.47 (0.44–0.49)	6,243	70.8	0.52 (0.49–0.55)	0.95 (0.88–1.01)
Milnacipran	1,979	62.3	0.38 (0.34–0.41)	817	57.4	0.33 (0.29–0.38)	1.15 (0.97–1.36)
Mirtazapine	5,136	66.1	0.40 (0.37–0.42)	3,210	65.4	0.44 (0.41–0.48)	0.93 (0.85–1.03)
Moclobemide	188	70.2	0.42 (0.31–0.58)	97	67.0	0.40 (0.27–0.63)	1.12 (0.65–1.89)
Paroxetine	40,908	75.1	0.68 (0.66–0.70)	21,986	75.5	0.75 (0.72–0.78)	**0.91 (0.88–0.95)**
Sertraline	11,310	73.9	0.66 (0.63–0.69)	5,579	74.1	0.71 (0.67–0.76)	0.94 (0.87–1.01)
Tianeptine	12,934	66.6	0.39 (0.37–0.40)	5,768	66.3	0.42 (0.40–0.45)	0.97 (0.90–1.03)
Trimipramine	257	63.4	0.38 (0.30–0.50)	118	61.0	0.37 (0.26–0.54)	1.05 (0.67–1.65)
Venlafaxine	22,217	72.3	0.61 (0.59–0.63)	10,698	71.8	0.63 (0.60–0.67)	0.97 (0.92–1.03)

[a]Binary logistic regression models with each medication (vs escitalopram) as the main predictor, adjusted for age, the presence of ≥1 chronic nonpsychiatric disease, specialty of the physician who prescribed the first antidepressant, and benzodiazepines or Z-drugs filled prescriptions (ie, ≥3 vs <3 filled prescriptions during the year of inclusion).
[b]Binary logistic regression models with each medication (vs all the other medications) as the main predictor with the addition of a sex by medication (vs all the other medications), adjusted for age, sex, the presence of ≥1 chronic nonpsychiatric disease, specialty of the physician who prescribed the first antidepressant, and benzodiazepines or Z-drugs filled prescriptions (ie, ≥3 vs <3 filled prescriptions during the year of inclusion).
[c]Boldface indicates aORs that were statistically significant after applying a Bonferroni correction.
[d]Not relevant given the small sample sizes (<100 in each group).
Abbreviation: aOR = adjusted odds ratio, NR = not relevant.

controlling for confounding factors and limits the comparability of treatment groups. For example, treatments perceived as most effective may be offered to the most affected patients, and differences in acceptability between medications in naturalistic studies may be explained by drug channeling. In addition, the inclusion of patients who had not received antidepressants in the previous year minimizes, but does not rule out, the depletion of susceptibility bias as antidepressant selection may be constrained among patients with a history of nonresponse or tolerability problems with other antidepressants. Although the analyses were adjusted for several potential confounders (ie, age, social deprivation, comorbid nonpsychiatric chronic conditions, specialty of the first prescriber, and filled prescriptions of benzodiazepines or Z-drugs), residual confounders cannot be excluded (eg, psychiatric condition severity, comorbid psychiatric conditions). Second, the SNDS did not generate information on the disorders motivating prescription of the antidepressants. Antidepressant medications are used to treat a wide variety of mental disorders, including MDD and anxiety disorders, obsessive-compulsive disorder, posttraumatic stress disorder, as well as nonpsychiatric conditions such as neuropathic pain for instance. Data from the literature suggest that about 55% of antidepressant first users may suffer from major depression or anxiety disorders in the 6 previous months.[37,45] Although we excluded the prescription of duloxetine and less than 1,500 mg per prescription for amitriptyline from our analyses, we could not exclude that other antidepressants were prescribed for neuropathic pain. Third, this database does not provide information on prescriptions not filled by patients.[46] However, failure to fill antidepressant prescriptions might be more likely related to general concerns about antidepressants (eg, fear of side effects, associated stigma) than to concerns about specific antidepressants and therefore is likely to be nondifferential across antidepressants. Fourth, this analysis does not provide data on actual drug consumption. However, it is unlikely that patients whose prescriptions are regularly filled do not take their medication. Fifth, the exclusion of people with at least one filled prescription for a mood-stabilizing or antipsychotic medication at baseline reduced but did not eliminate the risk of including patients with bipolar disorder or schizophrenia, but probably excluded some patients with unipolar depression as these medications

Figure 1.

Continuation/Change Ratio for Antidepressants in Men and Women[a]



[a]Antidepressants displayed were the most frequent of each classes.

can be used for augmentation. Sixth, low clinical acceptability was defined as a filled prescription of another antidepressant, an antipsychotic medication, or a mood stabilizer; this was presumed to indicate inadequate response or tolerability to the first antidepressant. However, the addition of an antipsychotic medication or a mood stabilizer could have also occurred because of a change in diagnosis (eg, bipolar disorder) or a worsening of the course of illness (eg, development of psychotic symptoms). However, in both cases, these developments could signal a failure of the first-line treatment, consistent with our definition. In contrast, we preferred not to merge "early termination" sequences with "change" sequences, because of uncertain clinical interpretability. Sex differences in "early termination" sequences might indeed depend on other aspects than efficacy and tolerability and may require further study. Seventh, since this database was based on first prescriptions occurring in 2011, it did not contain data about vortioxetine. Finally, although clinical acceptability encompasses both efficacy and tolerability,[47] we were unable to distinguish between the 2 in our results.

While the frequency of prescribing individual antidepressants reflects the prescribing habits of French

doctors, it is noteworthy that our proxy of acceptability is not based on the probability of prescribing any given medication as a first-line treatment. Instead, it is based on the likelihood of each medication being continued once prescribed as a first-line treatment. A striking example is sertraline, which was prescribed less frequently than tianeptine while having a largely higher acceptability in both men and women. Therefore, while sex differences regarding the acceptability of paroxetine and fluoxetine might explain to some extent sex differences in their prescription rates, the reverse is unlikely. Indeed, the rate of paroxetine prescriptions remained consistently 2-fold higher for paroxetine than fluoxetine for both men and women.

Interpretation of Findings

Compared to the well-established and substantial differences in the prevalence of anxiety disorders and MDD between men and women, sex differences in the acceptability of a first-line antidepressant treatment in the present study were small, consistent with the lack of compelling evidence in the literature.[24,25] Even if paroxetine and fluoxetine ranked differently across sex, the overall ranking was mostly similar, with escitalopram ranking first while agomelatine and tianeptine having poor acceptability. From a clinical perspective, it suggests that sex alone, with a few notable exceptions, might not be a basis for personalizing antidepressant drug treatment. From a research perspective, it suggests that the mechanisms underlying sex differences in the risk of anxiety or MDD may not drive sex differences in the efficacy or tolerability of antidepressant medications.

The 2 drugs that showed statistically sex differences in acceptability were also the 2 drugs with the largest known differential effect on weight gain.[48] Specifically, paroxetine has been associated with a greater risk of weight gain, while fluoxetine could even be associated with some weight loss.[48] As an explanatory hypothesis, weight gain might be associated with less acceptability in women than in men. Research among chronic users of antidepressants showed that over 50% of patients experienced adverse effects related to weight gain.[49,50] Weight gain has been identified as an important cause of early antidepressant discontinuation.[51,52] Depressed women generally experience greater weight gain than men.[22,53–56] Women are more likely than men to perceive themselves as too heavy for their height and report significantly more frequent overweight-related stigma experiences than men.[57,58] Women with overweight seem more likely than men with overweight to report weight dissatisfaction and attempts to lose weight.[59] These data are thus consistent with the hypothesis that weight-related concerns could explain sex differences in the acceptability of these 2 antidepressant medications. This illustrates the importance of accounting for acceptability, which combines both efficacy and tolerability, rather than efficacy alone as tolerability may be a major determinant of treatment maintenance and adherence, and thus of treatment outcome.

CONCLUSIONS

The ranking of first-line antidepressants according to their acceptability was almost similar between men and women in the present nationwide study, with escitalopram ranking first in both. Sex differences in antidepressant acceptability were observed with fluoxetine being more acceptable for men than for women and the reverse being observed for paroxetine. The greater weight gain liability of paroxetine over fluoxetine may account for this sex difference in medication acceptability. Should this hypothesis be confirmed in further studies, it suggests that weight-related concerns may be important in personalizing antidepressant treatment. These real-world data may help practitioners and policymakers prioritize choice of antidepressant medications in women and men.

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Supplementary Material

Article Title: Sex Differences in Antidepressant Acceptability According to Filled Prescription Sequences in a Nationwide Cohort Study

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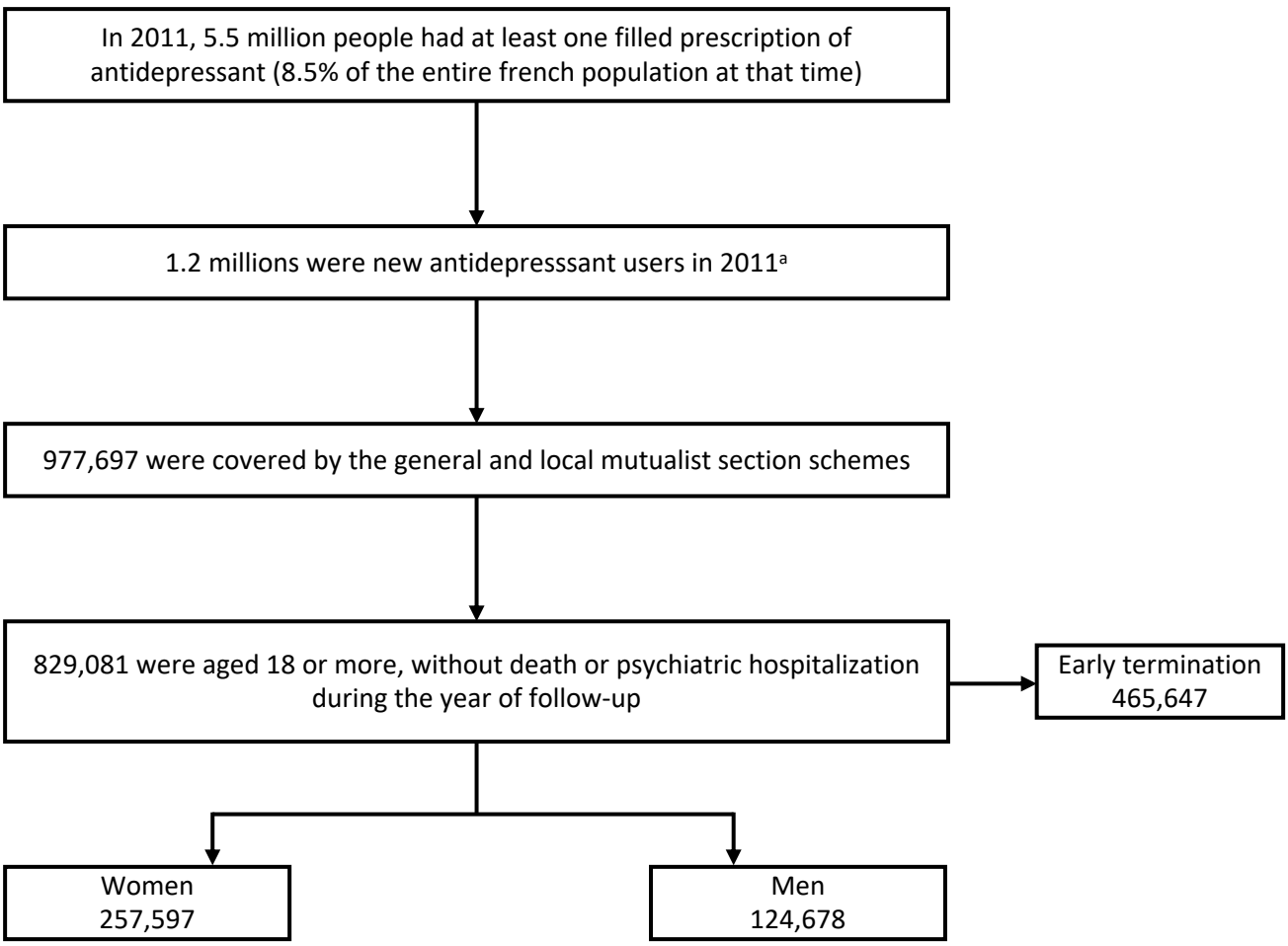
LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. **Figure 1** Flowchart
2. **Figure 2** Prescription Rates for Other Commonly Prescribed Antidepressants

DISCLAIMER

Supplementary Figure 1. Flowchart



[a] Individuals without psychiatric diagnosis identified in the past 4 or 5 years and without any prescription of a psychotropic drug in 2009 and 2010, except benzodiazepines and Z-drugs

Supplementary Figure 2. Prescription rates for other commonly prescribed antidepressants