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Supplementary Material

Article Title: Acceptability of Second-Line Antidepressant Medications Using Filled Prescription Sequences in a Nationwide Cohort Study

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List of Supplementary Material for the article

Disclaimer

This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary material

Supplementary appendix 1

This is a more complete version of the methods described in the original manuscript

About the SNDS

The SNDS collects the individual characteristics of all the beneficiaries of the various French national health insurance schemes, as well as filled prescriptions and procedures performed on an outpatient basis or in health care institutions and funded or reimbursed by the national health insurance [18,19].

Individual characteristics include age, gender, commune of residence (i.e. 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 an annual income below the poverty line in France[20].

A social deprivation index is also available at the scale of the commune, based on data published by the National Institute For Statistics And Economic Studies regarding household income, education level, occupational grade and unemployment rate. The higher the index, the higher the level of social deprivation [21].

Reimbursed drugs are identified according to the Anatomical Therapeutic Classification (ATC). Drugs dispensed during hospitalization are not reimbursed individually and cannot therefore be identified. The Caisse Nationale d'Assurance Maladie (CNAM), the general health scheme fund, has developed algorithms designed to identify 58 non-exclusive groups of health conditions (diseases, episodes of care, chronic treatments) using ICD-10 codes for long-term diseases (offering 100% reimbursement of health care) or hospitalizations, medications or medical procedures [22].

Study population

The main national health insurance scheme in France is the general scheme, which covers about 77% of the 66 million inhabitants, and this proportion reaches about 86% with addition of local mutualist sections beneficiaries. The other main schemes are the Mutualité Sociale Agricole (agricultural workers scheme) and the Régime Social des Indépendants (self-employed workers scheme), representing together almost 10% of the population and miscellaneous schemes (4%). This study was limited to general scheme with the addition of local mutualist sections beneficiaries due to lack of completeness of certain data in the other schemes during the study period.

Antidepressants were identified in the SNDS by ATC codes starting with “N06A”. Filled prescriptions of less than 1500 mg per prescription (i.e. 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 [23]. In France, there is no insurance restriction regarding the antidepressant medications used in this analysis.

In 2011, nearly 5.5 million people (all insurance schemes) had at least 1 antidepressant filled prescription from January 2011 to December 2011 and among them 1.2 million were defined as new antidepressant users in 2011. New users were defined by the absence of any prescription of a psychotropic drug in 2009 and 2010, except benzodiazepines (N05BA) and Z-drugs (N05CF01, N05CF02), together with no prior psychiatric diagnosis (i.e. a ICD-10 F code, excluding codes F00–F03) identified in the past 4 or 5 years from the CNAM algorithms (see above). Only people covered by the general and local mutualist sections schemes were selected resulting in 1 million participants. Next, exclusions were considered for people aged less than 18 years, death or psychiatric hospitalization occurring during the year of follow-up or those with at least one filled prescription of an antipsychotic medication or a mood-stabilizer. Finally, the source population included 863,513 participants (Figure 1, Supplementary Table 1).

Within this population, the study population was defined as patients who had at least 1 "change" sequence (Figure S1). Change sequence was defined as the delivery of a second-line treatment (switch or antidepressant combination therapy) within 6 months after at least 1 delivery of the first-line treatment).

Sub-populations were defined according to the first-line antidepressant treatment, using successively the therapeutic class (i.e., Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Noradrenaline Reuptake Inhibitors (SNRIs), alpha-2 blockers, tricyclic agents and other antidepressants (Others) and each individual molecule. To allow a twelve-month maximum follow-up period (6 months for both the first and second line), data were collected until December 2012.

The combination therapy sequences did not distinguish between augmentation and simultaneously introducing two antidepressants.

Primary outcome

According to the methods validated in the proof-of-concept study, the primary endpoint was the continuation/change ratio for second-line treatment (Figure S1). Continuation sequence was defined as at least 2 refills of the same antidepressant with no delivery of a different antidepressant over the 6-month period. Change sequence was defined as at least 1 delivery of a different antidepressant over the 6-month period.

Covariates

The following covariates were considered: age, sex, social deprivation index, CMU-C, specialty of the physician who prescribed the first antidepressant classified into three categories (general practitioners and hospital practitioners, psychiatrists private practice and other specialists private practice). Participants were considered as taking benzodiazepines or Z-drugs if they had

3 filled prescriptions or more during the year of inclusion. Participants with at least 1 chronic non-psychiatric disease were identified based on 48 groups of non-psychiatric diseases or non-psychotropic drugs of the above-mentioned algorithms.

Statistical Analysis

Categorical variables were described as percentages and continuous variables as means ± standard deviations (SD). All 95% confidence intervals (CIs) were calculated using non-parametric bootstrap sampling with percentile intervals. Multivariable binary logistic regression models were used to calculate adjusted odds ratios (aORs). All CIs were calculated using profile likelihood method (using glm() and confint() functions). The analyses were adjusted for age, sex, specialty of the physician, treatment by benzodiazepines or Z-drugs, and presence of at least 1 chronic non-psychiatric disease. Other covariates were only used for the descriptive or sensitivity analyses.

We then ranked second-line treatment according to their acceptability based on the same approach that we previously used for the first-line in the proof-of-concept study [17]. Because of the large sample size, we were able to carry out analyses from first considering intra-class switches, inter-class switches or combination therapy according to the first-line treatment class to considering each second-line medication according to each second-line medication. Unless otherwise specified in the results section, the reference category was the most prescribed treatment.

SAS Enterprise software version 7.13 (SAS Institute Inc, Cary, NC, USA) was used to create variables and extract data. All analyses were perfomed using R software, version 4.0.3.

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)* .

Supplementary Table 1. Characteristics of the population with incident antidepressant treatment according to the first line sequences of prescriptions during the first 6 months

	All	Sequence		
		Earlyt.	Cont.	Change
N	863,513	465,647	300,175	97,691
Row %	100.0	53.9	34.8	11.3
Female gender	66.4	65.0	67.5	66.6
Age (years)				
<30	13.8	16.7	9.5	13.1
30-39	18.7	19.7	16.7	20.1
40-49	21.2	20.8	21.1	22.8
50-59	17.6	16.9	18.6	18.3
60-69	10.8	10.4	12.0	9.3
70+	17.9	15.5	22.0	16.4
Deprivation index (quintiles) n = 799.999				
1 less deprived	18.0	17.1	19.3	18.4
2	18.9	18.3	19.7	18.8
3	19.9	19.6	20.2	20.2
4	19.9	20.0	19.9	19.5
5 more deprived	21.5	22.7	19.6	21.7
Overseas territories	1.8	2.3	1.2	1.3
CMU-C (<60 ans) n = 608393	11.3	12.8	8.6	11.5
First prescriber				
GP	90.0	91.7	88.4	86.5
Psychiatrist	5.9	4.1	7.4	9.5
Another specialist	4.6	4.2	4.1	4.0
At least one chronic Disease [a]	21.7	20.0	24.6	20.2
Drugs reimbursed [b]				
Z-drugs	14.7	12.9	16.3	18.1
Benzodiazepines	31.3	27.3	34.6	39.7
Mean (SD)				
Age	50.2 (19.7)	48.3 (20.5)	53.2 (18.6)	49.4 (18.0)

a, In the SNDS, algorithms identify 47 non-exclusive groups of chronic non-psychiatric diseases.
b, At least three filled prescriptions in the year of inclusion.

Abbreviations.
CMU-C = complementary health insurance coverage.
GP: General Practitioner.
SD: Standard Deviation.

Supplementary Table 2. Frequency and aOR of sequence categories by first-line class and second-line class

	First line class				
	SSRIs	SNRIs	Tricyclic agents	α2-blockers	Others
Second-line class	42,605 (66.8%)	8694 (13.6%)	2017 (3.2%)	4916 (7.7%)	5494 (8.6%)
SSRIs					
N	20952 (50.9%)	5615 (66.6%)	1002 (52.3%)	3029 (66.4%)	3660 (68.6%)
Continuation rate	61.4%	63.5%	53.4%	58.3%	62.2%
aOR (95% CI)	ref.	ref.	ref.	ref.	ref.
SNRIs					
N	10074 (24.5%)	844 (10.0%)	479 (25.0%)	621 (13.6%)	871 (16.3%)
Continuation rate	60.4%	57.3%	55.5%	52.0%	56.7%
aOR (95% CI)	0.97 (0.92-1.02)	**0.78 (0.67-0.90)**	1.08 (0.87-1.35)	**0.78 (0.66-0.93)**	**0.81 (0.70-0.94)**
Tricyclic agents					
N	1618 (3.93%)	443 (5.26%)	166 (8.7%)	191 (4.2%)	132 (2.5%)
Continuation rate	42.1%	43.1%	44.0%	46.1%	47.7%
aOR (95% CI)	**0.46 (0.42-0.51)**	**0.44 (0.36-0.54)**	**0.68 (0.49-0.95)**	**0.62 (0.46-0.83)**	**0.57 (0.40-0.81)**
α2-blockers					
N	4518 (10.9%)	777 (9.22%)	165 (8.6%)	338 (7.4%)	505 (9.5%)
Continuation rate	46.5%	46.2%	47.9%	55.9%	53.1%
aOR (95% CI)	**0.53 (0.50-0.57)**	**0.48 (0.41-0.56)**	0.79 (0.56-1.10)	0.91 (0.72-1.14)	**0.67 (0.57-0.81)**
Other antidepressants					
N	39.87 (9.7%)	751 (8.91%)	102 (5.3%)	383 (8.4%)	170 (3.2%)
Continuation rate	50.3%	47.7%	41.2%	53.9%	50.6%
aOR (95% CI)	**0.63 (0.58-0.67)**	**0.52 (0.44-0.60)**	**0.60 (0.39-0.90)**	**0.83 (0.67-1.03)**	**0.64 (0.47-0.87)**

Abbreviations.
aOR (95% CI): adjusted Odd Ratio (95% Confidence Interval), for age, sex, specialty of the first prescriber, treatment by benzodiazepines or Z-drugs, and presence of at least 1 chronic non-psychiatric disease
SSRIs: Selective serotonin reuptake inhibitors
SNRIs: Serotonin–norepinephrine reuptake inhibitors

Supplementary Table 3. Frequency of sequence categories by 1st line molecule and 2nd line molecule

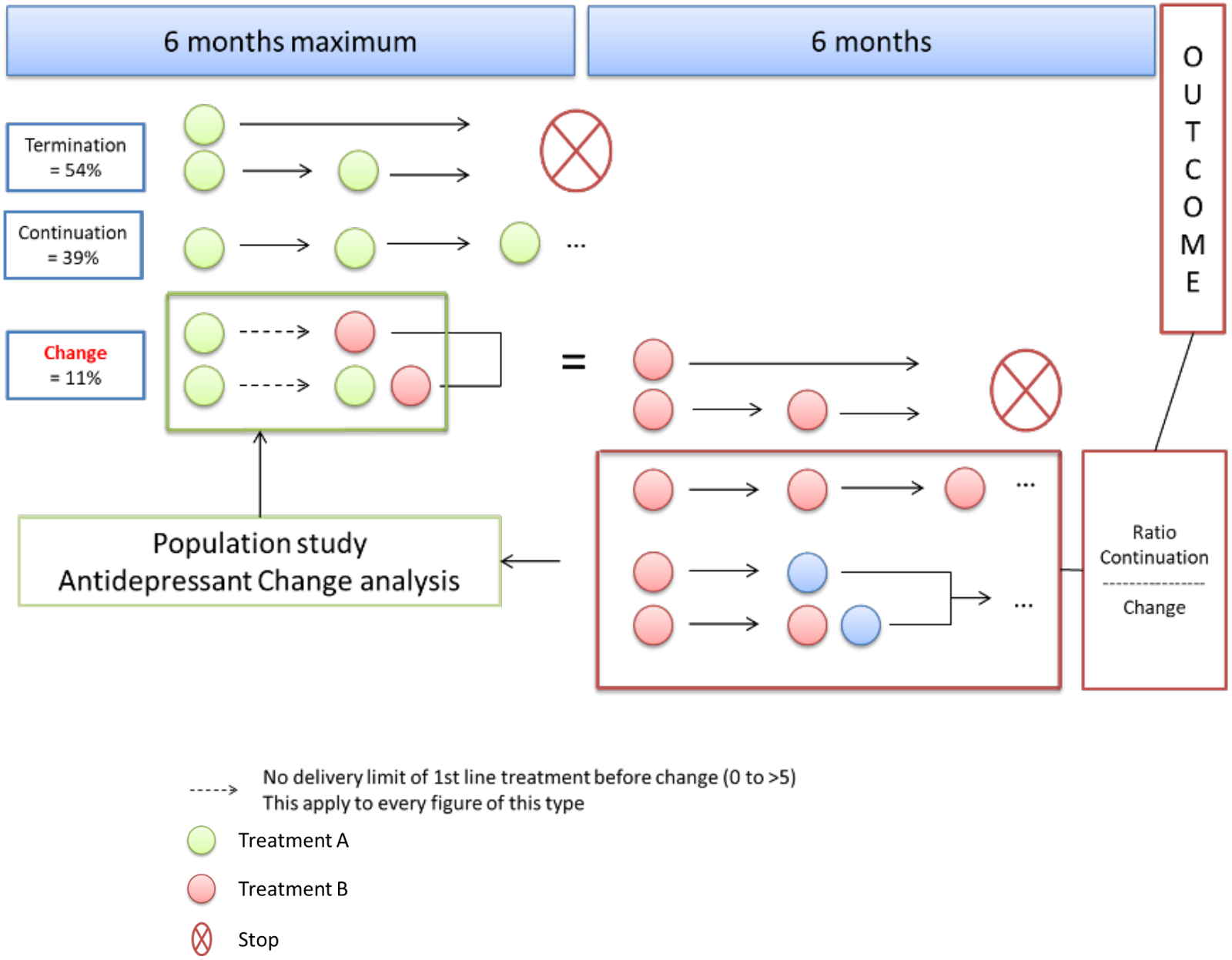
Second-line treatment	First-line treatment: ESCITALOPRAM N = 19,026 (29.9%)	FLUOXETINE N = 5144 (8.1%)	PAROXETINE N = 10,7566 (16.9%)	VENLAFAXINE N = 5266 (8.3%)	TIANEPTINE N = 4279 (6.7%)	MIANSERINE N = 3241 (5.1%)
ESCITALOPRAM						
N (%)		2017 (38.2%)	3282 (40%)	3556 (41.1%)	1394 (40.5%)	1352 (36.9%)
Continuation rate (%)		65.5%	67.2%	67.4%	65.8%	60.5%
aOR (95% CI)		ref.	ref.	ref.	ref.	ref.
VENLAFAXINE						
N (%)	3556 (20.0%)	475 (9.0%)	855 (10.4%)		288 (8.4%)	301 (8.2%)
Continuation rate (%)	63.5%	64.6%	60.9%		58%	59.2%
aOR(95% CI)	ref.	0.98 (0.82-1.18)	**0.77 (0.68-0.87)**		**0.73 (0.59-0.90)**	0.94 (0.71-1.26)
SERTRALINE						
N (%)	1046 (5.9%)	224 (4.2%)	404 (4.9%)	428 (5.0%)	139 (4.0%)	151 (4.1%)
Continuation rate (%)	61.7%	57.3	61.7%	61.5%	**67.6%**	54.6%
aOR (95% CI)	0.93 (0.80-1.07)	**0.74 (0.56-0.97)**	**0.80 (0.67-0.97)**	0.78 (0.58-1.04)	1.09 (0.76-1.58)	0.77 (0.53-1.13)
FLUOXETINE						
N (%)	2017 (11.4%)		855 (10.4%)	771 (10.9%)	218 (6.3%)	258 (7.0%)
Continuation rate (%)	61.5%		56.7%	57.3%	53.1%	55.8%
aOR (95% CI)	0.91 (0.81-1.02)		**0.64 (0.54-0.73)**	**0.66 (.53-0.81)**	**0.60 (0.46-0.77)**	0.83 (0.62-1.11)
PAROXETINE						
N (%)	3282 (18.5%)	1137 (10.9%)		1671 (29.3%)	656 (19.1%)	631 (17.2%)
Continuation rate (%)	58.8%	57.3%		60.1%	57.8%	58.8%
aOR (95% CI)	**0.81 (0.73-0.89)**	**0.69 (0.58-82)**		**0.73 (0.62-0.87)**	**0.70 (0.58-0.85)**	0.95 (0.76-1.18)
DULOXETINE						
N (%)	1293 (11.4%)	193 (3.7%)	331 (4.0%)	318 (12.0%)	147 (4.3%)	115 (3.1%)
Continuation rate (%)	54%	52.2	55.4%	46.9%	50.3%	46.1%
aOR (95% CI)	**0.67 (0.59-0.76)**	**0.58 (0.44-0.76)**	**0.62 (0.51-0.76)**	**0.60 (0.40-0.80)**	**0.54 (0.39-0.74)**	**0.55 (0.37-0.84)**
CITALOPRAM						
N (%)	1320 (7.2%)	377 (7.1%)	633 (7.7%)	649 (14.1%)	209 (4.5%)	273 (5.9%)
Continuation rate (%)	51.7%	63.1%)	57.6%	57.9%	57.0%	55.2%
aOR (95% CI)	**0.58 (0.51-0.66)**	0.88 (0.68-1.15)	**0.66 (0.56-0.78)**	**0.67 (0.52-0.86)**	**0.68 (0.52-0.89)**	0.81 (0.61-1.09)
MILNACIPRAN						
N (%)	381 (2.2%)	49 (0.9%)	74 (0.9%)	76 (0.9%)	38 (1.1%)	22 (0.6%)
Continuation rate (%)	47.%	54.8%	47.7%	48.2%	56.3%	42.4%
aOR (95% CI)	**0.52 (0.42-0.65)**	0.65 (0.39-1.09)	0.46 (0.34-0.62)	0.47 (0.30-0.73)	0.70 (0.39-1.27)	0.48 (0.23-0.97)
CLOMIPRAMINE						
N (%)	302 (1.7%)	40	74	35	8	
Continuation rate (%)	44.7%	40.4%	46.3%	45.5%	33.3%	46.3%
aOR (95% CI)	**0.46 (0.36-0.58)**	0.38 (0.25-0.57)	0.43 (0.31-0.60)	0.44 (0.27-0.69)	0.26 (0.10-0.59)	0.55 (0.29-1.04)
TIANEPTINE						
N (%)	1394 (7.9%)	280 (5.3%)	644 (7.9%)	452 (5.2%)		224 (6.1)
Continuation rate (%)	51.2%	47.2	51.5%	46.5		55.8%
aOR (95% CI)	**0.57 (0.50-0.64)**	**0.44 (0.33-0.59)**	**0.49 (0.41-0.58)**	**0.42 (0.32-0.54)**		0.83 (0.59-1.15)
MIANSERINE						
N (%)	1352 (7.6%)	231 (4.4%)	498 (6.1%)	250 (2.9%)	172 (5.0%)	
Continuation rate (%)	44.5%	36.4%	48.3%	49.8	53.1%	
aOR (95% CI)	**0.43 (0.38-0.49)**	**0.28 (0.21-0.37)**	**0.43 (0.36-0.51)**	**0.47 (0.37-0.61)**	**0.56 (0.42-0.74)**	
MIRTAZAPINE						
N (%)	978 (5.5%)	99 (1.9%)	208 (2.5%)	153 (1.8%)	74 (2.2%)	143 (3.9%)
Continuation rate (%)	49%	45.7%	46.7%	46.5%	55.3%	56.9%
aOR (95% CI)	**0.54 (0.47-0.62)**	0.43 (0.31-0.59)	**0.42 (0.34-0.52)**	**0.42 (0.31-0.56)**	**0.61 (0.44-0.86)**	0.88 (0.64-1.21)
AGOMELATINE						
N (%)	826 (4.7%)	75 (1.4%)	136 (1.7%)	122 (1.4%)	39 (1.1%)	67 (1.8%)
Continuation rate (%)	47.7%	47.3%	44.1%	44.1%	47.8%	56.7%
aOR (95% CI)	**0.53 (0.45-0.61)**	0.50 (0.34-0.74)	**0.39 (0.30-0.51)**	**0.39 (0.28-0.54)**	0.50 (0.34-0.72)	0.86 (0.50-1.47)

	Same continuation/change rate = reference (aOR not statistically significant different)
	Inferior Continuation/change rate compored to the reference(s) (2/3 < aOR ≤ 1)
	Inferior continuation/change rate compared to the reference(s) (0.5 < aOR ≤ 2/3)
	Inferior continuation/change rate compared to the reference(s) (aOR < 0.5)
	Insufficient data to conclude

Strategy/class/molecule with the largest sample size was chosen as reference for OR calculation

Abbreviations.
aOR = adjusted Odd Ratio for age, sex, specialty of the first prescriber, treatment by benzodiazepines or Z-drugs, and presence of at least 1 chronic non-psychiatric disease

Supplementary Figure 1. Study construction



Supplementary Figure 2. Evolution of continuation/change ratio between 1st and 2nde line treatment