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

Charles Ouazana-Vedrines, MD[a,*]; Thomas Lesuffleur, MSc[b]; Pierre Denis, MSc[b]; Nicolas Hoertel, MD, PhD[c]; Romain Olekhnovitch, PhD[d]; Mark Olfson, MD, PhD[e]; Carlos Blanco, MD, PhD[f]; Frédéric Limosin, MD, PhD[c]; Antoine Rachas, MD, PhD[b]; Philippe Tuppin, MD, PhD[b]; and Cédric Lemogne, MD, PhD[a]

## ABSTRACT

***Background:*** Although about half of patients do not respond to a first-line antidepressant medication, there is no consensus on the best second-line option. The aim of this nationwide population-based study was to rank antidepressants according to their relative acceptability (ie, efficacy and tolerability) using filled prescription sequences after failure of first treatment.

***Methods:*** About 1.2 million people were identified as new antidepressant users in the French national health data system in 2011. The inclusion criterion was having at least 2 filled prescriptions of a second-line treatment after a filled prescription of a first-line treatment, resulting in 63,726 participants. The outcome was clinical acceptability as measured by the continuation/change ratio for second-line treatment. Continuation sequence was defined as at least 2 refills of the same treatment. Change sequence was defined as at least 1 filled prescription of another antidepressant. Adjusted odds ratios (aORs) were computed through multivariable binary logistic regressions.

***Results:*** Intraclass switch had a better acceptability than interclass switch (aOR [95% CI]: 1.23 [1.20–1.28]). According to the first-line treatment, intraclass switch remained more acceptable for selective serotonin reuptake inhibitors only (1.37 [1.31–1.42]). For $\alpha_2$ blockers and tricyclic agents, combination antidepressant therapy was the most acceptable second-line option (1.59 [1.27–2.01] and 2.53 [1.53–4.04], respectively), whereas for serotonin-norepinephrine reuptake inhibitors, there was no significant difference between the strategies. For other antidepressants, intraclass switch had lower acceptability than interclass switch (0.70 [0.51–0.95]).

***Conclusions:*** Administrative claim databases may help with ranking acceptability of second-line treatments in real world settings and complement randomized controlled trials in informing clinicians about the most acceptable second-line options according to the first-line treatment.

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[a]Université Paris Cité, AP-HP, Hôpital Hôtel-Dieu, DMU Psychiatrie et Addictologie, Service de Psychiatrie de l'Adulte, INSERM, Institut de Psychiatrie et Neurosciences de Paris (IPNP), UMR_S1266, Paris, France

[b]Department of Pathologies and Patients, Caisse Nationale d'Assurance Maladie, Paris, France

[c]Université Paris Cité, AP-HP, Hôpital Corentin-Celton, DMU Psychiatrie et Addictologie, Service de Psychiatrie et d'Addictologie de l'Adulte et du Sujet Âgé, INSERM, Institut de Psychiatrie et Neurosciences de Paris (IPNP), UMR_S126, Issy-les-Moulineaux, France

[d]Population-based Epidemiological Cohorts Unit, UMS 011 Inserm-UVSQ, Villejuif, France

[e]Department of Psychiatry, New York State Psychiatric Institute/Columbia University, New York, New York

[f]Division of Epidemiology, Services and Prevention Research, National Institute on Drug Abuse, Bethesda, Maryland

**Corresponding author:* Charles Ouazana-Vedrines, MD, Service de Psychiatrie de l'Adulte, Hôpital Hôtel-Dieu, 1 Place du Parvis Notre-Dame, 75004 Paris, France (charles.ouazana-vedrines@aphp.fr).

Depressive and anxiety disorders are leading causes of disability worldwide.[1–4] Among pharmacologic interventions, antidepressant medications are recommended as the first-line treatment for unipolar major depressive episodes with moderate to severe intensity as well as for most anxiety disorders, apart from a specific phobia.[5–7] However, only about half of patients respond to a first-line antidepressant medication (ie, a reduction of at least 50% of the intensity of symptoms), and barely one third of those with major depression achieve symptom remission.[8–16]

The choice of a second-line treatment is thus a frequent and critical issue in clinical practice. Typical pharmacologic options are replacing the first medication with another (ie, a switch) or adding another medication to the first (ie, antidepressant combination therapy). Should a switch be selected, another important decision involves whether to choose the second-line antidepressant from the same or from another class. Unfortunately, there is no consensus to guide this decision.[12,13,17] One of the main reasons for this knowledge gap is that in light of the number of possible medication combinations, a randomized controlled trial (RCT) addressing this issue could not be sufficiently powered.[10] In addition, RCTs evaluating efficacy of antidepressants generally suffer from reduced external validity.[18–22] Administrative claims databases, which store large-scale data from routine clinical settings, may offer unique opportunities to address these issues.

After a first prescription of an antidepressant medication, the decision to refill the same prescription or to prescribe another medication reflects a clinical appraisal of the acceptability (or effectiveness) of the first prescription, which encompasses both efficacy and tolerability.[23] Indeed, if a response is observed without disabling side effects after 4 to 8 weeks, guidelines generally recommend continuing the same treatment for at least 6 months.[5,6,8,9] The present study is based on the hypothesis that sequences of filled prescriptions of antidepressants recorded in administrative claims databases can be used to rank different antidepressant medications according to their

**Clinical Points**

- Although about half of patients do not respond to a first-line antidepressant medication, there is no consensus on the best second-line option.
- The present study provides evidence that choice of second-line antidepressant treatment should be adapted to the first-line treatment that failed to be effective, as not all strategies are equivalent in terms of continuation of second-line treatment.

relative acceptability on a drug-by-drug basis. Specifically, acceptability would be captured for each treatment by the ratio of treatment sequences consistent with a continuation of the first prescribed treatment on those consistent with a change (either drug switch or combination). In a proof-of-concept study, we took advantage of the linkage of the French large-scale population-based CONSTANCES cohort study, which contains detailed individual data, with the SNDS (Système National des Données de Santé, French national health data system) database, which contains claims data from the national health insurance system.[24] We examined the association between sequences of filled antidepressant prescriptions and levels of depressive symptoms. This study demonstrated that patients who followed a "continuation" sequence had a lower level of depressive symptoms than those who followed a "change" sequence, as measured with the Center for Epidemiologic Studies-Depression (CES-D) scale. The score was significantly higher for participants with a switch sequence than for those with a continuation sequence, when CES-D was assessed during the 6-month period following the sequence onset, with no differences in the previous 6-month period.[24] This finding supports the view that the continuation/change ratio could be a clinically relevant proxy of the acceptability of the treatment and therefore could be used to rank different options, even in databases without measures of depressive symptoms.[24]

Based on the nationwide SNDS database, we used filled prescription sequences to rank second-line antidepressant options, as either strategies, classes, or medications, according to their continuation/change ratio after a failure of a first-line treatment.

## METHODS

A more complete version of the methods is displayed in Supplementary Appendix 1.

### About the SNDS

The SNDS collects the individual characteristics of all the beneficiaries of the various French national health insurance schemes, as well as a social deprivation index and all filled prescriptions and procedures performed on an outpatient basis or in health care institutions and funded or reimbursed by the national health insurance.[25,26] Algorithms allow identifying 58 non-exclusive groups of health conditions.[27]

### Study Population

In 2011, nearly 5.5 million people (all insurance schemes) had at least 1 antidepressant filled prescription, including 1.2 million new antidepressant users as defined by the absence of any prescription of a psychotropic drug in 2009 and 2010, except benzodiazepines and Z-drugs, together with no prior psychiatric diagnosis identified in the past 4 or 5 years.

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 1 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, 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 (Supplementary Figure 1).

Subpopulations were defined according to the first-line antidepressant treatment, first considering therapeutic classes (ie, selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], $\alpha_2$ blockers, tricyclic agents, and other antidepressants [others]), and then each individual molecule. In France, there is no insurance restriction regarding the antidepressant medications used in this analysis.

### Primary Outcome

The primary endpoint was clinical acceptability as measured by the continuation/change ratio for second-line treatment (Supplementary Figure 1). 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.[24]

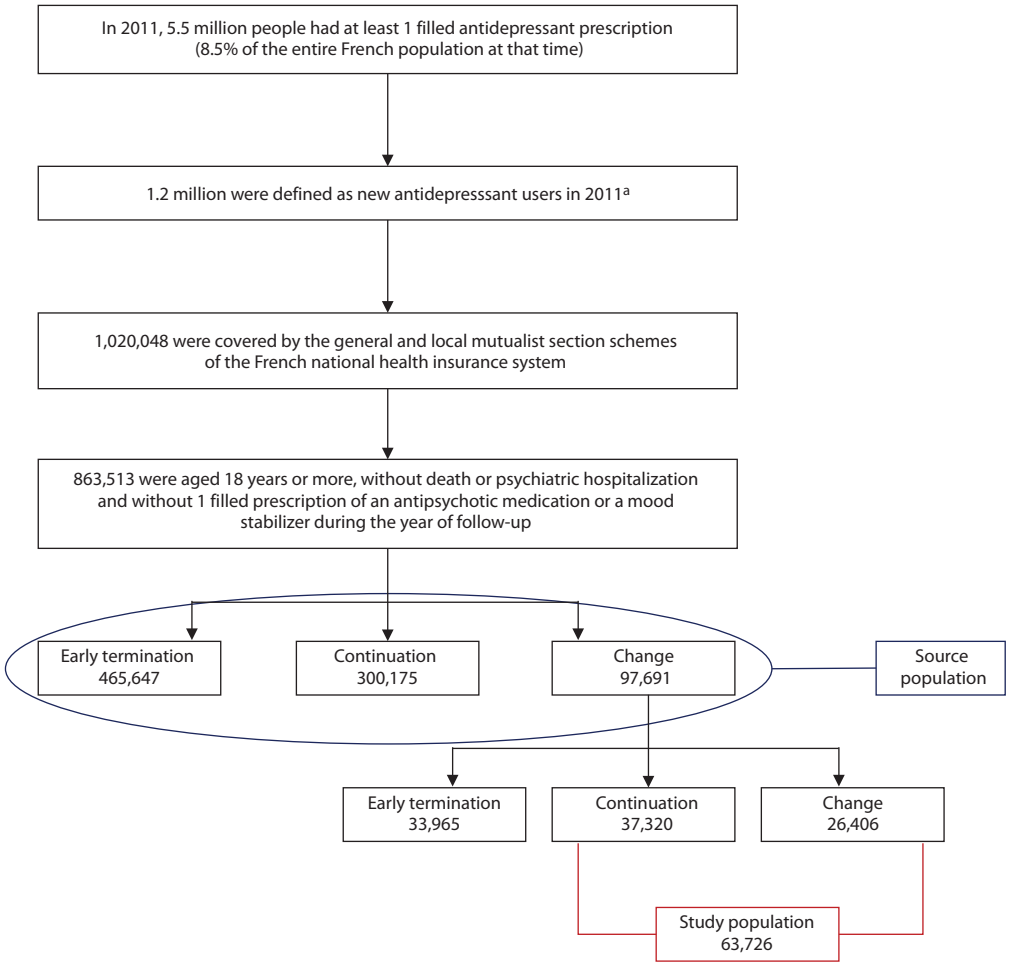
### Covariates

The following covariates were considered: age, sex, social deprivation index, benefit from complementary health insurance coverage (CMU-C), specialty of the physician who prescribed the first antidepressant as classified into 3 categories (general practitionerss and hospital practitioners, psychiatrists in private practice, and other specialists in private practice), benzodiazepines or Z-drugs intake (ie, participants with ≥ 3 filled prescriptions during the year of inclusion), and the presence of ≥ 1 chronic nonpsychiatric disease.

### Statistical Analysis

All 95% confidence intervals (CIs) were calculated using nonparametric 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

**Figure 1. Study Population Selection**




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

glm() and confint() functions). Due to missing data, social deprivation index and CMU-C were only used for descriptive or sensitivity analyses.

We then ranked second-line treatments according to their clinical acceptability, considering strategies (intraclass switches, interclass switches, or combination therapy), classes, or medications, in relation to the first-line treatment. Unless otherwise specified, the reference category was the most prescribed treatment.

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

The characteristics of the source population are displayed in Supplementary Table 1. A total of 97,691 individuals had a second-line treatment, switch or combination therapy, during the 6 months following the initiation of the first-line treatment. Six months after the introduction of the second-line treatment, 33,965 patients (34.8%) had only 1 or no refill ("early termination"), 37,320 (38.2%) had at least 2 refills ("continuation"), and 26,046 (27.0%) had at least 1 delivery of a different antidepressant ("change").

Therefore, our study population included 63,726 patients (66.9% women, mean age: 50.2 years) who experienced either a continuation or a change sequence after the introduction of the second-line treatment (Table 1). The first prescriber was most often a general or hospital practitioner (88%); 20.8% had at least 1 chronic non-psychiatric disease, and 19.2% had at least 3 filled prescriptions of a Z-drug and 41.7% of a benzodiazepine.

**Table 1. Characteristics of the Study Population (%)**

| | All (N = 63,726) | Continuation sequences (N = 37,320) | Change sequences (N = 26,046) | *P* value |
|---|---|---|---|---|
| Female gender | 66.9 | 67.3 | 66.5 | .047 |
| Age | | | | < .001 |
| < 30 y | 11.2 | 10.6 | 11.9 | |
| 30–39 y | 19.2 | 18.7 | 19.9 | |
| 40–49 y | 23.4 | 23.3 | 23.5 | |
| 50–59 y | 19.2 | 19.2 | 19.3 | |
| 60–69 y | 9.6 | 9.8 | 9.2 | |
| > 69 y | 17.4 | 18.3 | 16.2 | |
| Deprivation index (quintiles) (N = 57,978) | | | | < .001 |
| 1 (less deprived) | 19.3 | 19.6 | 19.0 | |
| 2 | 19.2 | 19.7 | 18.4 | |
| 3 | 20.3 | 20.2 | 20.4 | |
| 4 | 19.3 | 19.4 | 19.1 | |
| 5 (more deprived) | 20.1 | 20.2 | 21.8 | |
| Overseas territories | 1.1 | 1.0 | 1.2 | |
| CMU-C (N = 45,790) | 10.3 | 8.6 | 12.6 | < .001 |
| First prescriber | | | | < .001 |
| General practitioner | 87.5 | 88.2 | 86.6 | |
| Psychiatrist | 8.4 | 8.0 | 9.1 | |
| Another specialist | 4.1 | 3.8 | 4.3 | |
| At least 1 chronic disease[a] | 20.8 | 21.4 | 20.0 | < .001 |
| Drugs reimbursed[b] | | | | |
| Z-drugs | 19.2 | 19.0 | 19.5 | .11 |
| Benzodiazepines | 41.7 | 41.4 | 42.2 | .038 |

[a]In the Système National des Données de Santé (French national health data system), algorithms identify 47 non-exclusive groups of chronic non-psychiatric diseases.
[b]At least 3 filled prescriptions in the year of inclusion.
Abbreviation: CMU-C = complementary health insurance coverage.

Compared to people who were prescribed another antidepressant, those who continued the same antidepressant were more likely to be older, have had at least 1 chronic disease and have a general or hospital practitioner as their first prescriber and less likely to have received CMU-C, while tending to have a lower social deprivation index (Table 2). Although statistically significant, there were no substantial between-group differences regarding sex or filled prescriptions of Z-drugs or benzodiazepines.

Although the acceptability as measured by the continuation/change ratio of each medication decreased from the first- to the second-line treatment, the 6 treatments ranking first remained the same (Supplementary Figure 2).

### Ranking of Second-Line Treatment According to the Strategy

With interclass switch as the reference strategy, the continuation/change ratio of the second-line treatment was significantly higher for intraclass switch (aOR [95% CI]: 1.23 [1.20–1.28]) and for combination therapy (1.18 [1.10–1.27]) (Table 3).

We further refined our analyses according to the first-line class (Table 3). After an SSRI as first-line treatment, the ratio of the second-line treatment was significantly higher for intraclass switch (1.37 [1.31–1.42]) and combination therapy (1.16 [1.05–1.30]). After an SNRI as first-line treatment, there was no significant difference between the strategies. After a tricyclic agent as first-line treatment, the ratio of the second-line line treatment was significantly higher for combination therapy (2.53 [1.53–4.04]) and lower for intraclass switch (0.70 [0.51–0.97]). After an $\alpha_2$ blocker as first-line treatment, the ratio of the second-line treatment was significantly higher for combination therapy (1.59 [1.27–2.01]). After other antidepressants, the ratio was significantly lower for intraclass switch (0.70 [0.51–0.95]).

### Ranking of Second-Line Treatment According to the Classes

After an SSRI as first-line treatment, the continuation/change ratio of another SSRI as second-line treatment was significantly higher than for any other class, except for SNRIs (Supplementary Table 2, Figure 2). After first-line treatment with SNRI or other antidepressants, the ratio of an SSRI as second-line treatment was significantly higher than for all other classes. Following a tricyclic agent as first-line treatment, the ratio of an SSRI as second-line treatment was significantly higher than for another tricyclic or other antidepressants. After an $\alpha_2$ blocker as first-line treatment, the ratio of SSRI as a second-line treatment was significantly higher than for SNRI and tricyclic.

### Ranking of Second-Line Treatment According to the Medications

Given the high number of possible combinations (first-line medication × second-line medication = 529) and the small sample sizes for some combinations, we focused a priori on the 6 most commonly prescribed first-line treatments and the 13 most commonly prescribed second-line treatments. For escitalopram as first-line treatment, we also considered 2 frequent combination therapies with either mianserin or mirtazapine (both $\alpha_2$ blockers) (Supplementary Table 3).

Following escitalopram as a first-line treatment, the highest continuation/change ratio was observed with a switch to venlafaxine, with no statistically significant difference compared to a switch to sertraline, fluoxetine, or a combination of escitalopram with either mianserin or mirtazapine. After first-line treatment with fluoxetine, the highest ratio was observed for escitalopram as a second-line treatment, with no statistically significant difference compared to venlafaxine and citalopram. Following paroxetine as a first-line treatment, the highest ratio was observed for escitalopram as a second-line treatment. Following first-line treatment with venlafaxine and tianeptine, the highest ratio was observed for escitalopram as a second-line treatment, with no statistically significant difference compared to sertraline. After mianserin (ie, $\alpha_2$ blocker) as a first-line treatment, the highest ratio was for escitalopram with no statistically significant difference compared to the other second-line treatments except for duloxetine.

**Table 2. Frequency and Odds Ratio of Continuation (versus Change) Sequences by Covariables in the Study Population**

| | N | % Continuation | Univariate aOR for continuation |
|---|---|---|---|
| Gender | | | |
| Male | 21,036 | 57.2 | 1 |
| Female | 42,690 | 58.1 | 1.03 (1.00–1.06) |
| Age | | | |
| <30 y | 7,109 | 55.0 | 1 |
| 30–39 y | 12,240 | 56.6 | 1.07 (1.01–1.14) |
| 40–49 y | 14,882 | 57.6 | 1.11 (1.05–1.18) |
| 50–59 y | 12,253 | 57.5 | 1.11 (1.05–1.19) |
| 60–69 y | 6,122 | 59.4 | 1.20 (1.12–1.30) |
| >69 y | 11,120 | 60.8 | 1.26 (1.17–1.35) |
| Deprivation index (quintiles) (N=57,337) | | | |
| 1 (less deprived) | 11,216 | 58.8 | 1 |
| 2 | 11,106 | 59.7 | 1.04 (0.98–1.09) |
| 3 | 11,793 | 58.1 | 0.97 (0.92–1.02) |
| 4 | 11,183 | 58.5 | 0.99 (0.93–1.04) |
| 5 (more deprived) | 12,039 | 56.2 | 0.90 (0.85–0.95) |
| CMU-C | | | |
| No | 41,070 | 58.1 | 1 |
| Yes | 4,720 | 47.8 | 0.65 (0.61–0.68) |
| First prescriber | | | |
| General practitioner | 55,777 | 58.3 | 1 |
| Psychiatrist | 5,367 | 54.0 | 0.87 (0.82–0.94) |
| Another specialist | 2,582 | 54.9 | 0.88 (0.80–0.94) |
| Chronic disease[a] | | | |
| None | 50,449 | 57.4 | 1 |
| At least 1 | 13,277 | 59.4 | 1.09 (1.05–1.13) |
| Drugs reimbursed[b] | | | |
| Z-drugs | 12,285 | 57.1 | 0.97 (0.94–1.04) |
| Benzodiazepines | 25,587 | 57.4 | 0.97 (0.93–1.06) |

[a]In the Système National des Données de Santé (French national health data system), algorithms identify 47 non-exclusive groups of chronic non-psychiatric diseases.
[b]At least 3 filled prescriptions in the year of inclusion.
Abbreviations: aOR = adjusted odds ratio, CMU-C = complementary health insurance coverage.

### Sensitivity Analyses

For all rankings, sensitivity analyses including social deprivation index and CMU-C resulted in smaller samples but yielded similar results (data not shown).

## DISCUSSION

This nationwide study used filled prescription sequences to rank antidepressants according to their acceptability after a failure of a first treatment. From a source population of nearly 1 million new antidepressant users, significant differences in acceptability of second-line antidepressants were observed that contrast with results from available evidence from RCTs.[12,13,17] Comparing intraclass and interclass switches, intraclass switches were generally more acceptable than interclass switches, regardless of first-line class. However, this general pattern did not hold for all first-line treatments. Indeed, intraclass switch remained more acceptable for SSRIs only. For $\alpha_2$ blockers, combination therapy seemed to be the most acceptable, whereas for SNRI and tricyclic agents, interclass switch seemed most acceptable.

We then probed these sequences by second-line treatment. Not considering combination therapy, SSRI was the most acceptable second-line option after first-line treatment with SNRI or other antidepressants. SNRIs were not significantly different from SSRIs after first-line treatment by SSRI or tricyclic agents. Following first-line treatment with an $\alpha_2$ blocker, $\alpha_2$ blockers or SSRIs as second-line treatments had similar acceptability. As hypothesized, this picture should be further specified and depends on the specific antidepressant used in both the first and second lines.

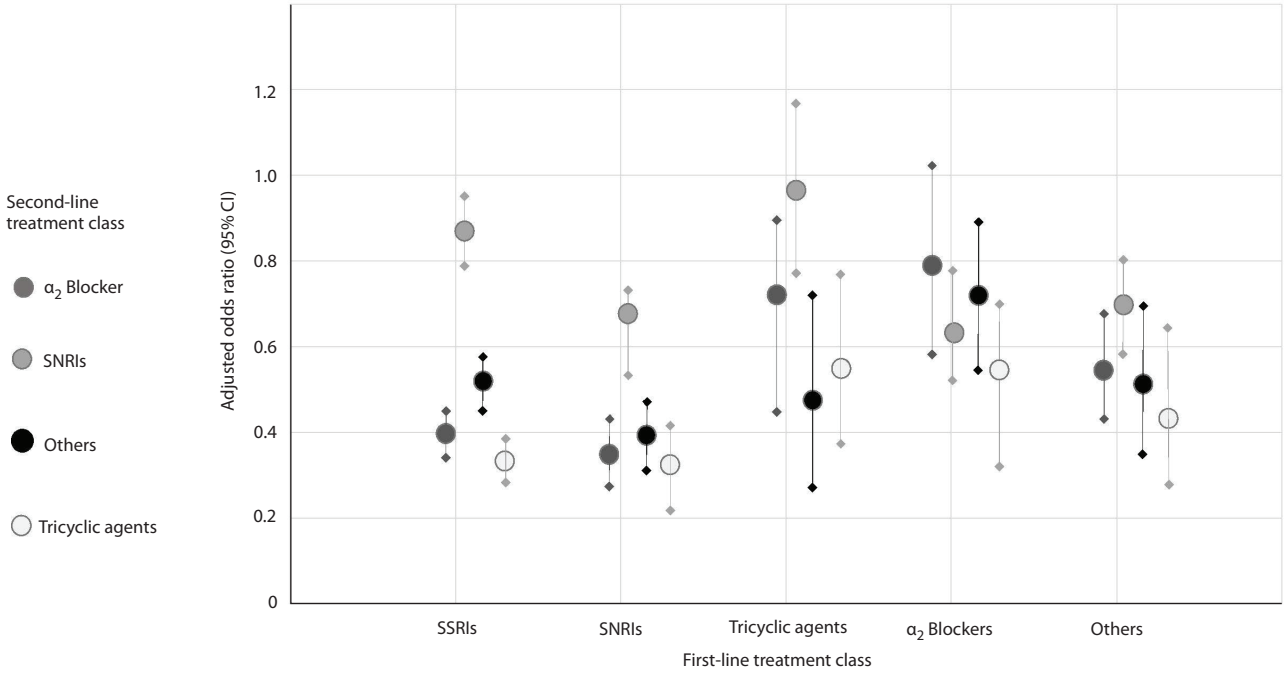
Escitalopram was almost always the most acceptable option as a second-line treatment, while venlafaxine was the most acceptable option after escitalopram as first line,

**Table 3. Frequency and aOR of Sequence Categories by First-Line Class and Second-Line Strategy**

| | First-line class | | | | | |
|---|---|---|---|---|---|---|
| Second-line strategy | All N=63,726 (100%) | SSRIs N=42,605 (66.8%) | SNRIs N=8,694 (13.6%) | Tricyclic agents N=2,017 (3.2%) | $\alpha_2$ Blockers N=4,916 (7.7%) | Others N=5,494 (8.6%) |
| Combination therapy | | | | | | |
| N (%) | 2,334 (3.7%) | 1,456 | 264 | 103 | 355 | 156 |
| Continuation rate | 59.9% | 57.1% | 61.0% | 73.8% | 66.5% | 60.3% |
| aOR (95% CI)[a] | **1.18 (1.10–1.27)**[c] | **1.16 (1.05–1.30)**[c] | 1.13 (0.88–1.47) | **2.53 (1.53–4.04)**[d] | **1.59 (1.27–2.01)**[d] | 1.07 (0.77–1.49) |
| Interclass switch | | | | | | |
| N (%) | 38,922 (61.1%) | 20,197 | 7,586 | 1,748 | 4,223 | 5,168 |
| Continuation rate | 55.9% | 53.8% | 59.0% | 52.7% | 56.4% | 60.0% |
| aOR (95% CI)[a] | ref | ref | ref | ref | ref | ref |
| Intraclass switch | | | | | | |
| N (%) | 22,470 (35.3%) | 20,952 | 844 | 166 | 338 | 170 |
| Continuation rate | 61.0% | 61.4% | 57.3% | 44.0% | 55.9% | 50.6% |
| aOR (95% CI)[a] | **1.23 (1.20–1.27)**[d] | **1.37 (1.31–1.42)**[d] | 0.94 (0.82–1.09) | **0.70 (0.51–0.97)**[b] | 0.98 (0.78–1.23) | **0.70 (0.51–0.95)**[b] |

[a]Adjusted odds ratio (95% confidence interval) for age, sex, specialty of the first prescriber, treatment with benzodiazepines or Z-drugs, and presence of at least 1 chronic non-psychiatric disease. Boldface indicates statistical significance.
[b]*P* value .05–.01.
[c]*P* value .01–.001.
[d]*P* value < .001.
Abbreviations: aOR = adjusted odds ratio, ref = reference, SNRIs = serotonin-norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors.

**Figure 2. Adjusted Odds Ratios of Continuation Versus Change of Second-Line Treatment Class by First-Line Class[a]**




[a]Circles are adjusted odds ratios and vertical bars are 95% confidence intervals of continuation vs change (reference: SSRIs as second-line treatment), adjusted for age, sex, specialty of the first prescriber, treatment by benzodiazepines or Z-drugs, and presence of at least 1 chronic non-psychiatric disease.
Abbreviations: SNRIs = serotonin-norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors.

though closely followed by sertraline and fluoxetine. Second-line treatments that seemed much less acceptable than the reference option also deserve attention. For instance, after first-line treatment with venlafaxine, second-line treatment with tianeptine or mianserin was prescribed in a number of cases equivalent to sertraline, but these treatments were clearly less acceptable (aORs < 0.5).

Strengths of the study include the large sample size, the duration of the follow-up, the representativeness of the population, and the generalizability of the results. In addition, this is the first study, to our knowledge, demonstrating a difference in the acceptability of second-line antidepressant treatments. Moreover, our study was sufficiently powered to examine these differences according to the first-line treatment. Finally, we were able to adjust our analyses for various potential confounding factors.

Some limitations should be acknowledged. First, the SNDS does not contain information about the disorders that warranted the prescription of antidepressant medications. Antidepressant medications are used to treat mental disorders other than major depression and anxiety disorders (eg, neuropathic pain). Data from the literature suggest that about 55% of first users of antidepressants may suffer from major depression or anxiety disorders in the previous 6 months.[24,28] Although we excluded the prescription of less than 1,500 mg per prescription for amitriptyline from our analyses, we could not exclude that other antidepressants (eg, duloxetine) were prescribed for neuropathic pain. However, tricyclic agents and duloxetine, which are the only drugs approved for this indication in France, were only 6.4% of the first-line prescriptions in the present study. On the other hand, we did not consider medications other than antidepressants that could be used in augmentation strategies (eg, antipsychotic medications). Second, this analysis does not provide data about actual medication consumption. However, it is unlikely that patients with regular filled prescriptions did not take their medication at all. Third, information about prescriptions that were not filled by patients was not available in this database. This population may represent up to 30% of individuals for whom antidepressants were prescribed.[29] However, failure to fill antidepressant prescriptions is more likely related to general concerns about antidepressants (eg, side effects, stigma) than to a concern about specific antidepressants and therefore likely to be non-differential across antidepressants. Therefore, the rate of failure to fill antidepressants should be the same across antidepressants and should not introduce substantial bias. Fourth, the exclusion of individuals with least 1 filled prescription of an antipsychotic medication or a mood stabilizer reduced the risk of including patients with bipolar disorder or any psychotic disease but probably excluded some patients suffering from unipolar depression with an augmenting strategy. As we could not ascertain the clinical diagnosis that warranted the prescription, including patients with antipsychotic or mood stabilizing medication would have resulted in greater clinical heterogeneity. Fifth, our study has limitations common to observational studies, including concerns over confounder control limiting the comparability of treatment groups with treatments perceived to be most effective proposed for the most affected patients.

One clear example of this limitation is the finding that a first prescription by a psychiatrist was associated with a higher risk of change, consistent with more severe patients receiving care from specialists. Psychiatrists, who are presumably more familiar with these medications, might be more likely to switch them to another, while general practitioners might be more comfortable with a smaller range of antidepressant medications. Sixth, although clinical acceptability might encompass both efficacy and tolerability,[23] we could not distinguish between efficacy and tolerability in our findings. Finally, considering the sample size, it is noteworthy that the statistical significance of the results is less important than their effect size and clinical relevance.

Although the frequency with which individual antidepressants were prescribed reflects the prescribing habits of French physicians, our methods were not based on the likelihood of any second-line treatment being prescribed. Instead, the acceptability ratios were based on the likelihood that the second-line treatment was continued once prescribed. A striking example is the case of sertraline, which was prescribed 4 times less often than paroxetine with a similar or even higher acceptability as first line. Our findings are based on data from the French National Insurance System, which covers nearly all the French population. Between-country differences in prescription practices may limit to some extent the generalizability of our results. However, the use of these data offers a unique opportunity to take in consideration real-life prescribing practices.

To our knowledge, mostly because of statistical power issues, there are no previous studies in the literature showing that one strategy is more acceptable than another in the management of depression resistant to first-line treatment.[12,13,17] While the relative clinical acceptability of antidepressants as second-line treatment may be substantially driven by their relative clinical acceptability as first-line treatment, our results suggest accounting for first-line medications when considering the acceptability of second-line treatments. Merging all the first-line treatments may result in a large effect size in one direction compensating a large effect size in the other direction that could explain the absence of significant results in the prior literature.

## CONCLUSION

The present study provides evidence that choice of second-line antidepressant treatment should be adapted to the first-line treatment that failed to be effective, as not all strategies are equivalent in terms of continuation of second-line treatment. This finding is noteworthy in the context of using administrative claims data to examine the effectiveness of antidepressants in real-life settings. Although RCTs are the gold standard to assess clinical efficacy of medical treatments, they have several limitations, including high costs, inability to evaluate complex treatments, and limited external validity that may result in sampling biases and limited generalizability.[21,30–32] In this context, supplementing RCTs results with evidence from observational studies and claims databases may help counterbalance these limitations to inform treatment decisions.[30] In particular, pharmacoepidemiologic research may yield insights regarding the effectiveness of medications in more broadly representative patient populations and for longer time periods.[10,33]

Similar results from RCTs and observational studies can increase the confidence in a therapeutic strategy, as suggested by a prior study that found little evidence that estimates of treatment effects in observational studies reported after 1984 are either consistently larger than or qualitatively different from those obtained in RCTs.[34]

This study was based on a method assessing the acceptability of antidepressant medications that could be used in other nationwide datasets. From a clinical perspective, if our results were to be confirmed by other studies, the findings would inform clinicians in the selection of second-line treatments for patients, according to their first-line treatment, their clinical history, as well as the pharmacologic characteristics of molecules, using a personalized approach. From a research perspective, it also opens opportunities to discover effective medication combinations that could lead to drug repositioning according to medical comorbidities.

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# Supplementary Material

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

**Authors:** Charles Ouazana-Vedrines, MD; Thomas Lesuffleur, MSc; Pierre Denis, MSc; Nicolas Hoertel, MD, PhD; Romain Olekhnovitch, PhD; Mark Olfson, MD, PhD; Carlos Blanco, MD, PhD; Frédéric Limosin, MD, PhD; Antoine Rachas, MD, PhD; Philippe Tuppin, MD, PhD; and Cédric Lemogne, MD, PhD

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## List of Supplementary Material for the article



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# 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

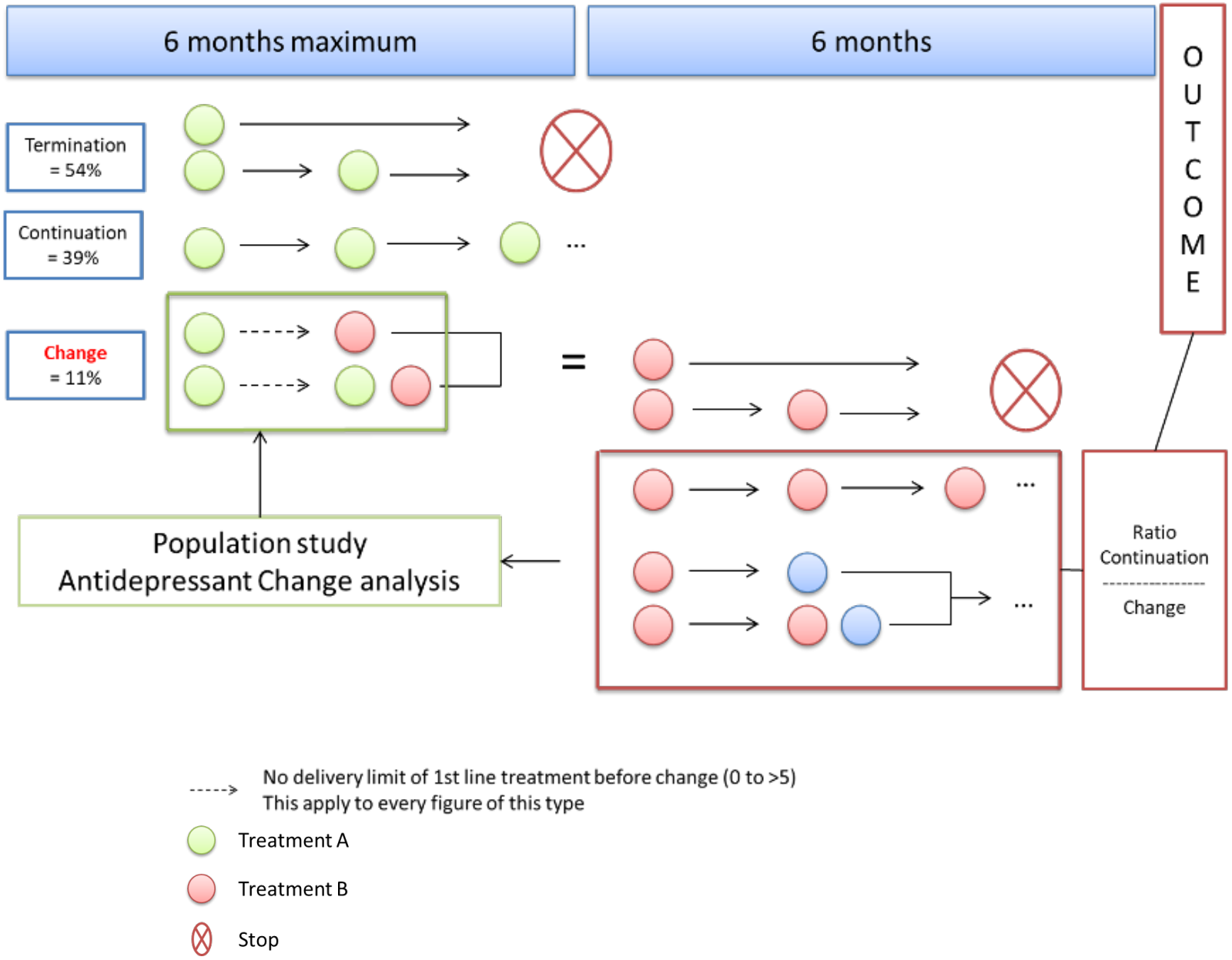
| | First-line treatment | | | | | |
|---|---|---|---|---|---|---|
| **Second-line treatment** | **ESCITALOPRAM** N = 19,026 (29.9%) | **FLUOXETINE** N = 5144 (8.1%) | **PAROXETINE** N = 10,7566 (16.9%) | **VENLAFAXINE** N = 5266 (8.3%) | **TIANEPTINE** N = 4279 (6.7%) | **MIANSERINE** N = 3241 (5.1%) |
| **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**