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Selective Serotonin Reuptake Inhibitors, are They All Equal? A Pharmacoepidemiological Study

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Abstract

Introduction: According to the French health authorities' guidelines relative to depression and anxiety disorder treatments, six Selective Serotonin Reuptake Inhibitors are available for prescription as a first-line of treatment. The guidelines suggest equivalence between these treatment options, but studies diverge regarding efficacy and safety profiles. Moreover, conditions in clinical trials are strictly controlled and do not truly reflect real life utilization. The objective of this study was to evaluate differences in efficacy and/or safety between these six selective serotonin reuptake inhibitors in real conditions of use.

Methods: Efficacy and safety were evaluated using a regional database of the French national health insurance. Patients who received a selective serotonin reuptake inhibitor for a new depressive disorder and who were compliant to the treatment for a period of at least 6 months were included. Events indicative of a lack of efficacy and/or safety during the 12-month follow-up period were identified in the database (i.e., a dose increase, a switch to another antidepressant drug or an association with another antidepressant drug). A Cox model was used to compare the frequency and the delay to onset of each type of indicative event for each selective serotonin reuptake inhibitor.

Results: Out of 3542 patients included, 1081 (30.5%) experienced an indicative event. The Cox model showed differences in terms of efficacy and safety. Patients treated with paroxetine, sertraline or citalopram as a first antidepressant were more likely to present a therapeutic failure than those treated by escitalopram or fluoxetine.

Conclusion: A Cox model identified differences between selective serotonin reuptake inhibitors in terms of efficacy and/or safety profile. Our study positioned Escitalopram as the most efficient and/or safe treatment option. This study strategy can viably be used to evaluate the real life usage and effects of other drugs, an essential part of post approval evaluation.

Keywords: Antidepressants; Cox model; Database

Abbreviations:

CNAM-TS: Caisse nationale d'Assurance Maladie des Travailleurs Salaries; **HAM-D:** Hamilton Rating Scale for Depression; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: Major Depressive Disorder; RCT: Randomized Clinical Trials; **SSRI:** Selective Serotonin Reuptake Inhibitor

Introduction

The prevalence of major depressive disorder (MDD) in the United States is estimated at more than 16% [1], and in France at close to 18% [2]. MDD is a serious psychiatric condition with a significant impact on public health. The medical burden of this pathology is tremendous: 70% of suicides are committed by depressed individuals, not treated nor diagnosed [3,4]. In this context, the efficacy and safety of medical treatments are essential. Current guidelines for the treatment of MDD recommend Selective Serotonin Reuptake Inhibitors (SSRIs) as a first line of treatment [5-7]. According to these guidelines, SSRIs are all considered as equivalent with respect to the risk-benefit balance. The recommended evaluation of efficacy and safety is to be done during the first eight weeks of treatment. The long term efficacy and safety of SSRIs has been shown [8].

SSRIs share one primary mechanism of action: Selective serotonin reuptake inhibition, via an inhibition of the presynaptic serotonin transporter SERT [9]. Following the administration of an SSRI, the first zone to experience a serotonin increase is the somatodendritic area of serotonin neurons. The consequence of this localized serotonin increase is the desensitization of auto receptors leading to an increase in the action potential of the neuron and in turn to an increase of serotonin release at the terminal axon. This process explains the perceived delay in action of SSRIs.

All SSRIs share this common mechanism of action, which explains the efficacy of this class. However, different individual reactions can be observed between SSRIs, concerning both efficacy and tolerance. This could be due to the distinct pharmacological properties of each SSRI [9-16].

- Fluoxetine is a 5-HT2c antagonist (which explains the "stimulant" effect), and a weak inhibitor of norepinephrine reuptake
- Sertraline is an inhibitor of the dopamine transporter and is also active on the sigma 1 receptor (contributing to an anxiolytic effects)
- Paroxetine is anticholinergic and is a norepinephrine reuptake inhibitor as well as a nitric oxide synthetase inhibitor (explaining source of sexual dysfunction)
- Fluvoxamine is active on the sigma receptor (contributing to an anxiolytic effect)
- Citalopram is a racemate composed of 2 enantiomers R-citalopram and S-citalopram, the efficacy of serotonin reuptake inhibition depends upon the S-citalopram [17]. R-citalopram has a moderate antihistaminic effect and a potential ECG QT increase
- Escitalopram is equivalent to the S-citalopram molecule, without the R enantiomer. It represents the "perfect SSRI" from a pharmacological point of view. Other SSRIs have different pharmacologic profiles and secondary binding properties

Although guidelines indicate that SSRIs can be prescribed indifferently as a first-line of treatment for MDD, randomized clinical trials and meta-analyses conducted over the last 10 years show diverse results with respect to efficacy and safety. The diversity of results is consistent with the different pharmacologic profiles describes above. Most randomized clinical trials (RCT) compared citalopram to escitalopram and none of them showed any significant difference between the two regarding safety. However, escitalopram was significantly more effective in 3 studies [18-20] while no significant difference was found in 2 studies [21,22]. Two of the 3 studies comparing escitalopram with paroxetine showed the superiority of escitalopram with respect to both safety and efficacy [3,23,24]. All other RCTs found no significant differences in safety or efficacy between SSRIs: escitalopram and fluoxetine [25,26]; citalopram and sertraline [27]; fluoxetine and sertraline [28]; fluoxetine, sertraline and paroxetine [29] and fluvoxamine, sertraline and paroxetine [30]. Meta-analyses [31,32-36] have also been published, two of them did not find any differences between SSRIs, while the others concluded with the superiority of escitalopram.

Inconsistent conclusions between studies generate uncertainty concerning differences in efficacy and safety among SSRIs. Moreover, conditions of use in clinical trials are strictly controlled (compliance, observance, highly selected populations) and do not reflect real life usage.

We accomplished an analysis based on the French national health insurance database to assess the efficacy and safety of SSRIs in real life conditions of use. We compared the occurrence and the delay in the apparition of events that could reflect a lack of efficacy and/or safety of the main SSRIs among compliant outpatients (treated for a period of at least 6 months with antidepressants) at the onset of their treatment (during the first 3 months of treatment).

Materials and Methods

Database

Data was obtained from the health insurance database of the Caisse Nationale d'Assurance Maladie des Travailleurs Salariés (CNAM-TS) of the Pays de la Loire region (a region of western France). With a population of 3.5 million inhabitants the Pays de la Loire region is the fifth largest in France. All health insurance data relative to inhabitants affiliated to social security (all employed inhabitants) are available in the database.

Study population

All patients over the age of 18 starting an antidepressant monotherapy of SSRIs for a new MDD, were included and followed for a period of 12 months (Figure 1).
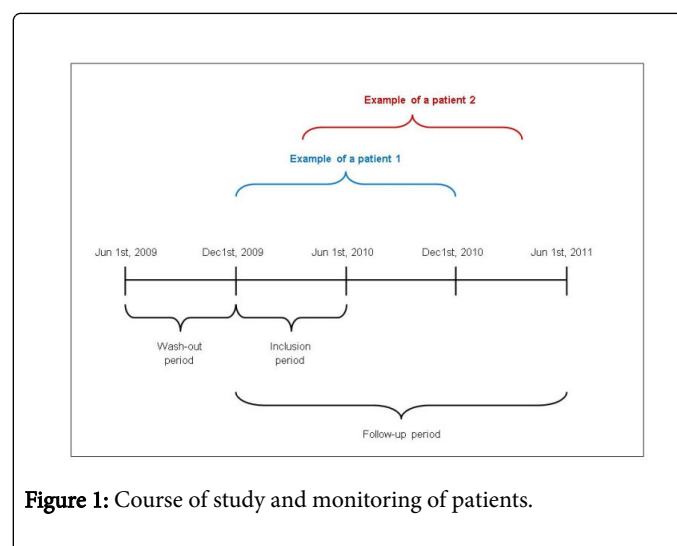

Figure 1: Course of study and monitoring of patients.

A patient was considered as starting an antidepressant monotherapy by SSRIs for a new depressive episode if the following criteria was met (Figure 2):

- At least one recorded reimbursement for one of the six SSRIs, between December 1, 2009 and June 1, 2010 (inclusion period)
- Absence of a reimbursement for any antidepressant treatment during the six months prior to inclusion
- Compliance [37] to recommended SSRIs prescription defined by both a duration of antidepressant treatment consistent with a depressive episode and a time between two prescription renewals consistent with uninterrupted treatment
- Treatment for a period of at least 6 month from the date of inclusion [5] even if antidepressant treatment was switched to another SSRI or to a different pharmacological class of antidepressant
- No interruption in prescription for longer than 42 days between renewals, including changes in antidepressant treatment to another SSRI or to a different pharmacological class of antidepressant. In France antidepressants are prescribed for 28 days, 42 days is one and half this prescription duration.
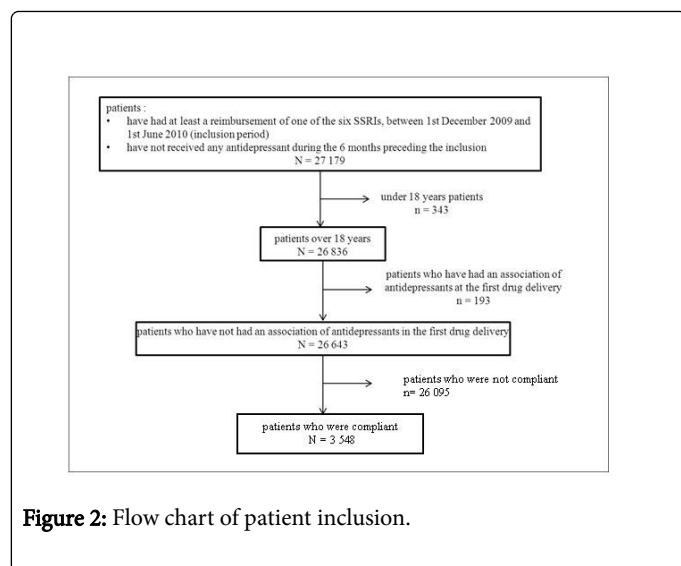
Figure 2: Flow chart of patient inclusion.

Follow-up

Inclusion period was from December 1st, 2009 until June 1st, 2010. Reimbursements for each patient included were followed for 12 months. Figure 1 shows the course of the study and the monitoring of patients.

Comparison between SSRIs

According to the current guidelines for the management of depression [5-7], the evaluation of efficacy and safety of antidepressant treatment should be done at an early stage following the start of treatment (during the first eight weeks of treatment). After having verified compliance and adherence to the prescription, if poor therapeutic response is observed, medical practitioners have three second-step treatment options:

- Increase in antidepressant dosage
- Switch to another antidepressant
- Combination of antidepressants

If a patient develops side effects, medical practitioners will logically change the treatment and switch to another antidepressant.

We chose to use these three criteria as they form the treatment strategy recommended in the French health authorities' guidelines for the management of depression [5]. It is clearly stated that in case of a lack of efficacy or a resistant depression, practitioners should either increase the dosage of antidepressant treatment, or switch to another antidepressant, or combine antidepressants.

Each of these events (dosage increase, switching to another antidepressant or combination with another antidepressant) was considered as indicative of the primary endpoint of a lack of efficacy and/or safety of the antidepressant treatment. In cases where several events occurred, we focused on the time between the first antidepressant delivery and the first event.

Statistical analysis

All statistical analyses were performed with SAS (version 9.3). The significance level was set at 0.05.

Descriptive analysis

Descriptive statistics were used to characterize patients at baseline with respect to demographic and clinical measures.

Cox model

A Cox proportional hazard model [38] was constructed to assess and compare the timing of events between different SSRIs. This model considered the "survival" time as the time before the occurrence of an event (an increase in dosage or a switch to a new antidepressant) after initiation prescription of a SSRI. The multivariate Cox model estimated hazard ratios of the effect of each variable adjusted to the other variables [39].

In order to focus on the first three months of SSRI prescription and to be consistent with the standard practice of evaluation of an antidepressant treatment, data was censored at 3 months. The assumption of a proportional hazard was checked by testing the interaction between time and all other variables in a univariate Cox model. For all variables this assumption was adhered to.

Event detection and date

In case of an occurrence of a new antidepressant (a switch or a combination of antidepressants) the date of the event was considered to be the date of prescription of the new antidepressant.

To detect dose increases, we developed an algorithm. A dose increase was considered when a dose threshold that took into account the smallest existing pharmaceutical form of an antidepressant was exceeded (for instance 5 mg, 10 mg, 15 mg and 20 mg exist for escitalopram the dose taken into account was thus 5 mg). Thresholds were specific to each SSRI.

The algorithm was based on average dosage across three deliveries. This technique allowed us to smooth the averages which are sensitive to the variation in time between two deliveries. In cases of dose increase, the event date was that of the second delivery.

In case of the occurrence of several events the earliest one was considered.

Variables used for adjustment

The Cox model was adjusted by:

- Age: Split into four categories: 18-35 (reference); 36-55; 56-75 and >76
- Gender: Male (reference); female
- Prescription by a psychiatrist: No (reference); yes
- Treatment for another neuro-psychiatric illness (antiepileptic, thymoregulator, antipsychotic): No (reference); yes
- Long-term psychiatric illness: No (reference); yes
- Anxiolytic treatment: No (reference); yes
- Hypnotic treatment: No (reference); yes
- SSRI primo-prescribed, categorized into five classes: Escitalopram (reference), fluoxetine, paroxetine, sertraline, citalopram. Patients with fluvoxamine primo-prescription were excluded because the population sample was too small. Patients were classified into one of these mono-therapy treatment groups based on the first SSRI they received.

Results

Descriptive statistics

Selection process and population size: A total of 27,179 patients had at least one prescription for one of the 6 SSRIs in the database. After applying the inclusion criteria, the final cohort included was 3,548 patients. Figure 2 shows the study flow-chart. We excluded patients who were prescribed fluvoxamine as a first line of antidepressant treatment because the sample size was too small in this group (N=6). Thus, a total of 3,542 patients were included in the study.

Baseline characteristics: Table 1 shows the baseline characteristics of the population with respect to the first prescribed antidepressant. 70% of included patients were women, this is consistent with prior studies.

The majority (45.7%) of the population was aged between 36 and 55 and the average age was 51.3 years. Few patients (5.2%) were treated for a long-term psychiatric illness, which is consistent with the medical management of outpatients, although 16.2% of patients had at least one prior psychiatric prescription.

The most commonly prescribed first antidepressant was escitalopram (44.8%), followed by paroxetine (26.9%) and fluoxetine (12.6%). Anxiolytic treatment was combined with an antidepressant in 68% of cases, in contrast with hypnotic treatment which was combined with antidepressant in 30% of the cases. Very few patients (0.9%) received an opiate maintenance treatment. During the first 3 months of SSRI prescription, 1% (N=35) of patients had a dose increase as a first event, whereas 13% (454) had an occurrence of a new antidepressant (switch or a combination of antidepressants).

	Escitalopram n (%)	Paroxetine n (%)	Fluoxetine n (%)	Citalopram n (%)	Sertraline n (%)	Total n (%)
Total N	1568 (44.8)	953 (26.9)	446 (12.6)	272 (7.7)	285 (8.0)	3542
Age (years)						
18-35	238 (15.0)	153 (16.1)	54 (12.1)	27 (9.9)	42 (14.7)	514 (14.5)
36-55	737 (46.5)	403 (42.3)	234 (52.5)	123 (45.2)	121 (42.5)	1618 (45.7)
56-75	409 (25.8)	253 (26.6)	128 (28.7)	73 (26.8)	78 (27.4)	941 (26.6)
76 and over	202 (12.7)	144 (15.1)	30 (6.7)	49 (18.0)	44 (15.4)	469 (13.2)
Gender: Female	1094 (69.0)	662 (69.5)	354 (79.4)	191 (70.2)	186 (65.3)	2487 (70.2)
Prescription by a psychiatric	286 (18.0)	121 (12.7)	69 (15.5)	54 (19.9)	42 (14.7)	572 (16.2)
Long term psychiatric illness	100 (6.3)	51 (5.4)	14 (3.1)	10 (3.7)	12 (4.2)	187 (5.3)
Anxiolytic treatment	1083 (68.3)	671 (70.4)	302 (67.7)	180 (66.2)	184 (64.6)	2420 (68.3)
Hypnotic treatment	550 (34.7)	276 (29.0)	138 (30.9)	89 (32.7)	83 (29.1)	1136 (32.1)
Treatment for opioid dependence	13 (0.8)	6 (0.6)	3 (0.7)	4 (1.5)	7 (2.5)	33 (1.0)
Dose increase as first event during the first 3 months of prescription	16 (1.0)	10 (1.1)	3 (0.7)	2 (0.7)	4 (1.4)	35 (0.99)
Occurrence of a new antidepressant as first event during the first 3 months of prescription	187 (11.8)	127 (13.3)	56 (12.6)	44 (16.2)	40 (14)	454 (12.8)
Total of patients who presented an event during the first 3 months of prescription	203 (12.8)	137 (14.4)	59 (13.2)	46 (16.9)	44 (15.4)	489 (13.8)

Table 1: Population baseline characteristics by first prescribed antidepressant.

Model results

Table 2 shows the analysis of event occurrence (switching, combining or dosage increase) using the multivariate Cox model censored at 3 months, the results of the Cox model identified a significantly higher probability of an event for patients who received paroxetine (HR=1.25), citalopram (HR=1.46) sertraline (HR=1.40) compared to escitalopram. Patients who took paroxetine, citalopram or sertraline were more likely to have a dose increase, a switch in therapy or the addition of an antidepressant in the first 3 month of the prescription than those who took escitalopram.

The Cox model identified a significantly higher probability of events for patients with at least one prior psychiatric prescription (HR=2.29), or for patients with an addition of an anxiolytic (HR=2.31) or a hypnotic drug (HR=1.83). Moreover, we found a significantly lower rate of events for patients aged between 56 to 75 (HR=0.68).

Figure 3 shows the adjusted survival graph [40], during the first 3 months of treatment, where patients with escitalopram or fluoxetine

were less likely to have an early dosage increase or therapy switch or the addition of a new antidepressant than those with paroxetine, sertraline or citalopram.

Parameters	Hazard Ratio	95% CI	P
Age (years)			
18-35	Reference	-	-
36-55	0.94	0.74-1.20	0.64
56-75	0.68	0.51-0.91	0.009
76 and more	0.75	0.51-1.09	0.13
Gender			
Male	Reference	-	-
Female	1.03	0.85-1.26	0.73
Prescription by a psychiatrist			
No	Reference	-	-
Yes	2.29	1.87-2.79	<0.0001
Long term psychiatric illness			
No	Reference	-	-
Yes	0.74	0.49-1.11	0.14
Treatment for another neuro-psychiatric illness			
No	Reference		
Yes	1.22	0.97-1.52	0.08
Anxiolytic treatment			
No	Reference	-	-
Yes	2.31	1.80-2.96	<0.0001
Hypnotic treatment			
No	Reference	-	-
Yes	1.83	1.53-2.20	<0.0001
SSRI primo-prescribed			
Escitalopram	Reference	-	-
Paroxetine	1.25	1.01-1.55	0.04
Fluoxetine	1.08	0.81-1.44	0.61
Citalopram	1.46	1.06-2.02	0.02
Sertraline	1.40	1.01-1.94	0.04

Table 2: Analysis of event occurrence (switching or combining or increasing dose) using the multivariate Cox model censored at 3 months.
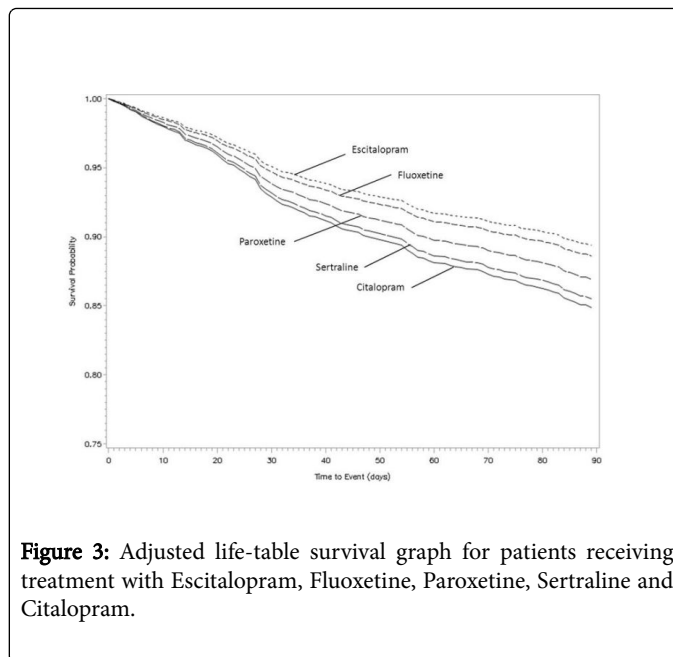

Figure 3: Adjusted life-table survival graph for patients receiving treatment with Escitalopram, Fluoxetine, Paroxetine, Sertraline and Citalopram.

Discussion

Our study was based on a group of 3,542 compliant patients who were included from a pool of 27,179 and who began SSRI treatment.

Among these 3,542 patients, during the first 3 months of prescription 13.8% had an increase in dosage, a switch or were prescribed a combination of antidepressants. The times to apparition of failure events during the first 3 months of treatment were compared using a Cox model. Our results show that, patients treated with paroxetine, sertraline or citalopram as a first line of antidepressant were more likely to present an early therapeutic failure than those treated with escitalopram or fluoxetine. Moreover, the time to event occurrence was affected by specific covariates: prescription by a psychiatrist, combination with an anxiolytic or a hypnotic treatment. All these covariates seem to suggest a more severe disorder.

For the comparison of SSRIs we chose guideline criteria. These criteria, described below, are specified in both European and French guidelines [5,7]. Indeed, the French health authorities guideline [5] provides clear recommendations in case of a lack of efficacy and/or resistant depression. Practitioners have a choice of one of the following strategies (i) increase in antidepressant dosage (ii) switch to another antidepressant (iii) combining antidepressants. With these criteria, we included a relatively small part of the database in order to focus on patients with a clear prescription, good compliance and sound follow-up. As we included patients from the onset of their treatment for a new depressive episode, the treatment was prescribed for a minimum of 6 months, even if a complete remission of symptoms was observed during the first 6 months. As it is unlikely that any patient would have completely healed and consequently stopped taking treatment during the first three months, our criteria were therefore evaluated during this time frame.

We included patients with good compliance across the six months of treatment and thus a time between two prescription renewals consistent with treatment without discontinuation. This methodological choice is consistent with guidelines [7] which

recommended as a first step, the verification of adherence to treatment in cases where patient's symptoms do not adequately respond to initial pharmacological interventions. This was of great importance: as our objective was the comparison between SSRIs, we had to be sure that patients had a high rate of compliance.

Our methodological choices implied the inclusion of 15% of the total data base patients. Although in some respects non pragmatic, we chose to evaluate our criteria on a selected cohort in order to limit bias. We aimed at comparing the efficacy between populations who were able to take their medication appropriately, a gap between renewals meant that a patient did not have enough drugs to take them daily as prescribed. The excluded patients represented 85% of total patients. These patients also need to be evaluated. The reason for their non-adherence to inclusion criteria requires assessment: Both in cases of a decrease in dosage (possibly due to side effects or to complete remission), or gaps between renewals. Both could also be a marker of poor therapeutic response. These situations are out of the health authorities guidelines but have to be taken into account. However, the French health insurance database is not tailored to this type of assessment for which clinical data is also required. Our study is therefore not representative of all patients, but is representative of compliant patients.

Our results show the existence of two groups of antidepressants among SSRIs: Escitalopram and fluoxetine on one side and paroxetine, sertraline and citalopram on the other.

The superiority of escitalopram over other SSRIs has been demonstrated in head to head efficacy trials and meta-analyses [18-20,22,23,32-34]. Escitalopram is the most specific SSRI, because of its unique pharmacological property: selected serotonin reuptake inhibition [11]. This high specificity may result in less side effects and a better tolerance profile. The superiority of escitalopram over citalopram is explained by the fact that it is the active S-enantiomer of the racemic [41] citalopram drug. The action on serotonin reuptake inhibiting resides in the S-citalopram [17], the R-enantiomer of citalopram may in fact even counteract the action of the S-enantiomer [42] in citalopram. Moreover, the presence of R-citalopram in citalopram can be responsible for antihistaminic effects and a QT increase.

No significant differences were found between fluoxetine and escitalopram. A pharmacological hypothesis explaining this result could be that fluoxetine is the only 5-HT2C receptor antagonist SSRI [11]. This antagonism prevents serotonin action and impedes the inhibition of noradrenaline and dopamine release. Fluoxetine is an SSRI but also a disinhibitor of noradrenaline and dopamine. This property confers to fluoxetine a significant antidepressant action and could explain treatment continuation despite possible side effects.

We can assume, based on this pharmacoepidemiological study, and as it has already been reported in literature, that it could be preferable to use escitalopram as a first line of treatment. Moreover, fluoxetine is a CYP 2D6 inhibitor, this can lead to pharmacokinetic interaction with other drugs, like antalgics. However, each patient is singular, and the therapeutic choice should be individual, integrating all the clinical parameters of a patient. The efficacy profile of paroxetine and sertraline could be explained by the inhibitory properties of the norepinephrine and dopamine uptake.

The increase in dosage represent only 1% of the events encountered. Facing an insufficient therapeutic response, practitioners may therefore in fact prefer to associate another antidepressant or switch to a different antidepressant at an early stage of treatment. However, if therapeutic response is incomplete but seems to exist, practitioners are tempted to wait a short while before concluding that a true partial response has occurred and increase dosage.

According to the French guidelines [5], anxiety and MDD management are related and pharmacological strategies in case of treatment failure is similar. In this respect, we can consider that SSRIs are comparable in terms of medical use. In France all SSRIs are prescription-only drugs and are all reimbursed, consequently the health insurance database is true, complete and accurate. All reimbursement information was available and we did not have any missing data. Most previous studies are efficacy trials conducted in highly selected populations and the applicability of their results to real-life patient could be limited. In contrast, we did not select patients according to any criteria of comorbidity, placebo-response, depression severity or drug dependence. We wanted to study the effectiveness in a population that reflects the real-life outpatient population [43]. Previous studies examined response on diagnostic depression scales such as the HAM-D (Hamilton Rating Scale for depression) or MADRS (Montgomery-Åsberg Depression Rating Scale). Changes on such scales could be viewed as intermediate outcomes but might not always be related to changes in health [35]. Proxies that appear without fail when treatment is ineffective and that we were able to spot across the database were found. These pragmatic outcomes measure real insufficient therapeutic response and enrich the results obtained with depression scales.

The first study weakness is that available data was reimbursement data and not consumption data, the included population was considered as compliant based on two parameters: treatment duration and the time between two renewals. Thereby, we introduced a selection bias: going to the pharmacy and obtaining repeat prescriptions is not enough proof that the pills have actually been taken. Thus some patients considered as compliant in our study could in reality have had repeat prescriptions but without taking the pills. Secondly, data was obtained from regional reimbursement database which covers a large majority of the population but excludes some populations, as farmers and the self-employed. We could therefore question the representativeness of the study population and whether or not efficacy of SSRIs could be population dependant. A link between depression severity and efficacy on one hand and the depression severity and population on the other hand could be possible. The study population is on a whole similar to the French population in terms of age and sex distribution, median income and unemployment rate.

Conclusion

Our study is pioneering from a methodological point of view and contributes to the existing literature regarding comparison among SSRIs in outpatients. We used a survival analytical approach which is generally considered to be the most rigorous and sensitive in detecting differences between antidepressant efficacy [44] and we focused on pragmatic outcome measures across a national health insurance database. This study contributes to reflections on a potential hierarchy among SSRIs and could be confirmed by larger pharmacoepidemiology studies with greater population representativeness and more clinical outcomes. Finally, comparison could be extended by integrating into the model other pharmacological classes of antidepressants. Comparison of drug efficacy from national health insurance databases should be developed and validated in order to facilitate research and provide reliable results.

Funding

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