Master of Public Health

Master international de Santé Publique

Evergreening: How Green is it after all?

Ali Al-khafaji

2010-2011 MPH Year 2

INSERM U738, Centre d'Epidémiologie Clinique, Hôpital Hôtel-Dieu, Paris, France

Professional Advisor

Prof. Philippe Ravaud and Ludovic Trinquart

INSERM U738, Centre d'Epidémiologie Clinique, Hôpital Hôtel-Dieu, Paris, France

Academic Advisor

Dr Moise Desvarieux

Mailman School of Epidemiology, Columbia University, New York, USA

Acknowledgments

I’m deeply grateful to Prof. Philippe Ravaud, who is the origin behind the idea of this project, for giving me the privilege and the opportunity to be part of an amazing team and for his guidance and supervision during my internship period.

I would like to thank Dr. Moïse Desvarieux for his support, friendship and advice in and out of the internship framework.

This project and report would not have seen daylight, if it was not for the help, guidance and friendship and “awesomeness” of Ludovic Trinquart. The statistic tricks I learned and the innovative ways of motivation helped me the most when I was feeling down. The challenge of time constraint or like Ludovic likes to call them “my laziness” were never to be overcome ,if it was not for the teamwork performance and help from Adeline Abbé and Marie Dalichampt to finish the project in time.

During this internship, I was sponsored by the Ecole des Hautes Etudes en Santé Publique. Also, I would like to thank Prof. Martine Bellanger for her help and support during the Master program.

Last but not least, I’m grateful for my family’s support and love, especially during my master degree studies.

Abstract

Background: The evergreening practices have long been known. There is paucity of data quantifying the clinical and financial drawbacks of such strategies.

Objective: To perform a relative efficacy assessment as well as reimbursement cost evaluation for a case study of evergreening.

Methods: citalopram and escitalopram, the chiral switching of the former drug, were studied. To assess their relative efficacy, we performed a systematic review and meta-analysis of head-to-head trials. We also performed a systematic review of placebo-controlled trials of citalopram or escitalopram to estimate the contrast using indirect comparison meta-analysis. The search for trials was based on an overview of reviews, an examination of FDA reviews, HAS Commission de la Transparence reviews, and pharmaceuticals' trials registers. To assess reimbursement costs, we analyzed the French national health insurance information system (SNIIR-AM). Individual data for citalopram, its generic drugs, and escitalopram from 2004 up to 2010 were retrieved from the representative Echantillon Généraliste des Bénéficiaires sample. Consumption (in numbers of prescriptions and of defined daily doses) and costs trends were assessed.

Results: For the assessment of the relative efficacy, the meta-analysis of the 6 identified head-to-head RCTs showed superiority of escitalopram over citalopram (combined odds ratio 1.54, 95% CI, 1.26 to 1.87). The funnel plot did not reveal any asymmetry, but our search proved the existence of three missing head-to-head trials. Based on 10 citalopram and 12 escitalopram placebo-controlled trials, the adjusted indirect comparison did not show any difference between citalopram and escitalopram (indirect combined odds ratio 1.03, 95% CI, 0.83 to 1.28). There was no evidence of publication bias for placebo-controlled trials based on funnel plots and asymmetry tests. The inconsistency between direct and indirect evidence was significant. For the reimbursement cost assessments, data for 37391distinctive insurees (about 7% of the EGB sample) were retrieved, cumulating 358355 reimbursements from 2004 to 2010. The numbers of prescriptions and defined daily doses purchases showed a sharp decrease in the citalopram consumption, while escitalopram illustrated a substantial increase during the same timeframe. The reimbursement costs for escitalopram continued to grow to reach 2,727,547 Euros in 2010, compared to a decrease in the cost burden for citalopram (130,996 Euros).

Conclusion: The discrepancy in direct and indirect efficacy comparison is likely explained by publication bias among head-to-head trials. Escitalopram may not bring benefit compared to citalopram, while maintaining delays in generics introduction and preventing a substantial cost saving.

Résumé

Contexte: Les stratégies «d'evergreening» sont connues depuis longtemps. Peu de données évaluant les conséquences cliniques et financières de ces stratégies sont disponibles.

Objectif: Effectuer une évaluation de l'efficacité relative ainsi que des coûts de remboursement pour un couple de médicaments représentatif des stratégies d'evergreening.

Méthodes: le citalopram et l'escitalopram, la version énantiopure du premier, ont été étudiés. Pour évaluer leur efficacité relative, nous avons effectué une revue systématique et méta-analyse d'essais face-face. Nous avons également effectué une revue systématique des essais comparant citalopram ou escitalopram à placebo, afin de les comparer via une comparaison indirecte ajustée. La recherche des essais a été basée sur l'examen de revues antérieures, des rapports d'évaluation de FDA et de la Commission de la Transparence (HAS) ainsi que des registres d'essais des laboratoires. Pour évaluer les coûts de remboursement, nous avons analysé le SNIIR-AM. Les données individuelles pour le citalopram et l'escitalopram à partir de 2004 jusqu'en 2010 ont été enregistrées à partir de l'Echantillon Généraliste des Bénéficiaires. L'évolution de la consommation (évaluée en nombres de prescriptions et de doses quotidiennes déterminées) et des coûts a été évaluée.

Résultats: Pour l'évaluation de l'efficacité relative, la méta-analyse des 6 essais face-face identifiés a montré la supériorité de l'escitalopram sur le citalopram (odds ratio combiné 1,54, IC95%, de 1,26 à 1,87). Le funnel plot n'a révélé aucune asymétrie, mais notre recherche a prouvé l'existence de trois ECR face-face manquants. Basée sur 10 et 12 essais contre placebo pour le citalopram et l'escitalopram, la comparaison indirecte ajustée n'a pas montré de différence entre les 2 (odds ratio combiné indirecte 1,03, IC95%, de 0,83 à 1,28). Les funnel plots et les tests d'asymétrie n'indiquent pas de possibilité de biais de publication. L'incohérence entre les estimations directe et indirecte était significative. Pour l'évaluation des coûts de remboursement, les données de 37391assurés (7% de l'EGB) ont été enregistrées (358355 remboursements de 2004 à 2010). L'analyse des nombres de prescriptions et de doses quotidiennes déterminées a montré une forte diminution de la consommation de citalopram, alors que l'escitalopram montrait une augmentation importante. Les coûts de remboursement pour l'escitalopram ont continué de croître pour atteindre 2727547 euros en 2010, comparativement à une diminution de la charge des coûts pour le citalopram (130.996 euros).

Conclusion: L'écart important entre estimations directe et indirecte s'explique probablement par le biais de publication affectant les essais face-face. L'escitalopram n'apporte probablement pas de bénéfice par rapport au citalopram. Sa présence sur le marché retarde vraisemblablement l'introduction de médicaments génériques qui permettrait elle-même une économie importante pour l'Assurance Maladie.

Keywords

Evergreening; Patent laws; Meta-analysis; Health Insurance; Escitalopram; Citalopram

Abbreviations

AFSSAPS	Agence Française de Sécurité Sanitaire des Produits de Santé
CEPS	Comité Economique des Produits de Santé
CIP	Code Identifiant de Présentation
CT	Commission de la Transparence
DARE	Database of Abstracts of Reviews of Effectiveness
DDD	Daily Defined Dose
EGB	Echantillon Généraliste de bénéficiaires
EMBASE	Excerpta Medica Database
FDA	Food and Drug Administration
HAMD	Hamilton Depression Rating Scale
HAS	Haute Autorité de Santé
ITT	Intention to Treat
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major Depressive Disorder
RCT	Randomized clinical trial
SNIIR-AM	Système National d'Informations Inter-Régimes de l'Assurance Maladie
SSRI	Selective Serotonin reuptake inhibitors
TRIPS	Trade-Related Aspects of Intellectual Property Rights
UNCAM	Union Nationale des Caisses d’Assurance Maladie
UNOCAM	Union Nationale des Organismes de Complémentaires
WHO	World Health Organization

Table of Contents

1 Introduction

1.1 The Concept of Evergreening

As the world strives for a balance between reward for innovation and encouraging the dissemination of knowledge by disclosing the information, patent emerged as one of the legislations that have been adapted to create that desired balance; in the pharmaceutical industry, patent is a monopoly granted by the authorities to the inventor of a drug (pharmaceutical companies) for an innovation for a defined period of time.(1) Patent gives the exclusive right to a patentee to prevent others from making, using, selling, or distributing the patented invention without permission.(2)

Evergreening, although not a formal legal concept, is a term referring to the numerous strategies in which patent owners, from pharmaceutical products, use patent laws to extend their monopoly privileges beyond periods that are normally allowed by law.(3) This practice is also known as drug lifecycle management, layering, double patenting or “Me-too” medications.(4) Typically, the attempts to extend the brand name’s market share for a longer period are done late in the patent life and on high-revenue earning drugs (“blockbuster medications”).(5) The practice of evergreening is frequent, the National Institute for Health Care Management reported that as many as 674 (65%) of 1,035 new drugs approved by the FDA from 1989 through 2000 were modified versions of existing drugs; only 361 (35%) were of new molecular entities.(6)

The filing of patent extension claims by the pharmaceuticals could be on the originated version of the medication on the bases of having new indications or a new additional components pertaining to the medication, or they could be filing a new patent claim on a revised formula of the originated drug having the same indications.(7) Usually those claims are based on incremental modifications of a drug, based on its pharmacokinetic properties: modifications of drug release into the body, methods of administration rather than on alteration in the chemical entities, also increasing the purity of the active pharmaceutical ingredient has proved to be a promising means of extending patent protection. For instance, AstraZeneca is converting its proton-pump inhibitor franchise from Prilosec to Nexium, the *S*-enantiomer of Prilosec, in an effort to preserve its sales from the imminent patent expiration of Prilosec.(8) Some of the other evergreening strategies include: usage of a different salt or molecule as an additive to the main drug components, active metabolite extraction and chiral switching.(9, 10)

Besides the former methods mentioned, there are legislative ways to delay the generic drug introduction to the market and extend the market exclusivity for the patent holder.(11) One of

those methods is the 30-month stay provision also known as the Hatch-Waxman Act, when the brand holder can litigate on the term that the generic producer violated one of the components listed under the patented brand, and this automatically prevents the FDA from approving the generic drug for 30 months or until the litigation is resolved or the patent lapses.(3, 12) The Trade-Related Aspects of Intellectual Property Rights (TRIPS) has not helped a lot in stopping pharmaceuticals from continuing to pursue evergreening techniques. Under TRIPS, patents must be granted for at least 20 years, presumably, the World Health Organization (WTO)'s time-frame to sufficiently remunerate an inventor. However, few Research and Development firms would opt to lose their monopoly, therefore trying to extend the patent's privilege duration.(13, 14)

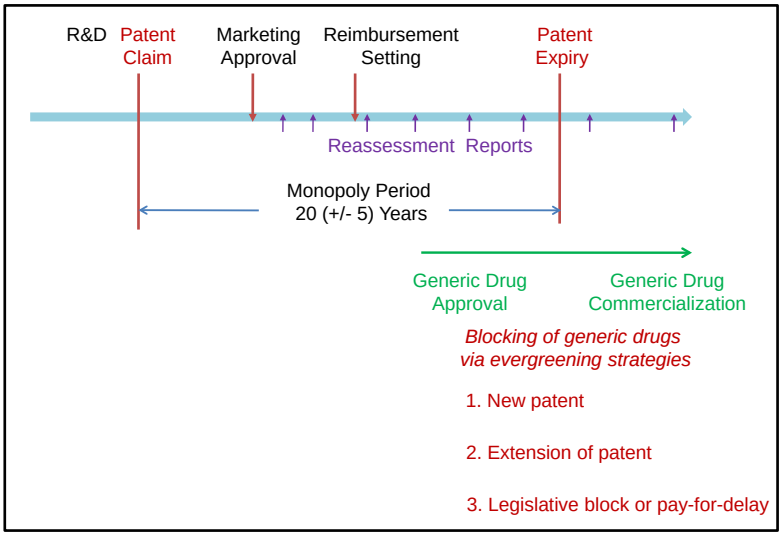
1.2 Implications of Evergreening

One of the main drawbacks of evergreening strategy is the delay of entry of generic drugs into the drug market. This comes from the fact that patent rules do not make a distinction between inventions consisting of "brand new product " and inventions pertaining to improvements.(15, 16) This, eventually, forces the generic manufacturers to choose between waiting for all the patents to expire and applying for marketing authorization, or running the risks of litigation and the associated costs and delays.(13, 17) In 2002, an extensive investigation by the US Federal Trade Commission found that as many as 75 % of new drug applications by generic drug manufacturers were the subject of legal actions under patent laws by the original brand-name patent owner.(18) These were driving up US drug costs by keeping the cheaper generic versions off the market. While those practices are completely legal, this represent an immense burden on generic companies in terms of competitiveness and drug development; as well as, increases the health system expenditure and scale up patient co-payments.(18) Pharmaceuticals defend evergreening practices and claim that revised formulas provide significant benefits to the drug industry, so by allowing patents for secondary developments, the patent system provides incentives for companies which may not have the commercial or scientific capability to invent and develop new chemical entities to engage in incremental innovation.(7)

In France, medications' cycle starts with a pharmaceutical manufacturer claiming patent on a molecule after years of research and clinical trials. The duration of the patent monopoly can go up to 25 years; this would include the marketing approval time and the administrative phase.(19) The administrative phase could span over an average period of 3 years, during which, the efficacy and benefit gained efficacy are evaluated by the *Commission de Transparence*, while the reimbursement price and rate are fixed by the *Union Nationale des Caisses d'Assurance Maladie, Comité Economique des Produits de Santé* and *Union Nationale des Organismes de Complémentaires*.(20) After the date of patent expiry is

reached, the market share is open to the competition of generic drugs produced by other pharmaceutical firms. However, evergreening strategies could be implemented at this time period to extend the duration of monopoly privileges of the patent holder (figure 1).

Figure 1: drug lifecycle



The scarcity of data and studies covering evergreened medications, where main source of data come from court records, legislative and governmental reports(21), is one of the main obstacle to further unravel this practice and try to expose the truth behind it. Meanwhile, economic analyses about the cost difference for reimbursement and consumption changes between the evergreened couple are based mainly on projections, which are not sufficient to accurately estimate the cost burden of evergreening behavior. Moreover, fiscal constraints had led to a closer scrutiny of medication with similar mechanisms to those of standard reference.(22)

For example, UK estimated the cost burden resulted in patent consumption changes if the generic drugs happened to be launched to the market, with the assumption of 50% drop in the usage of the patent medication to the generic medication, and the assumption that generic drugs are 50% cheaper than the patent drugs, at the time when the patent expires, the cost difference would be around 164 million pounds. The same calculations were done with the assumption of 75% drop in the price and that generic drugs will take over 75% of the market share, and the cost would be around 369 million pounds difference.(5, 9)

1.3 A case study of evergreening

Depressive disorders are commonly associated with decreased in the quality of life, impaired daily activities and worsened medical outcomes.(23)The World Health Organization estimates that, by 2030, major depressive disorder (MDD) will be second only to ischemic heart disease as an overall cause of disability and disease burden.(24)The burden of

depression in France is high with the disease prevalence reaching 7,8 %, while 3,4% presented with sever depressive episode.(25) In addition, the high consumption of antidepressant medication is France is substantial with a figure of 50 defined dosed per day per 1000 inhabitant in 2007.(25)

Citalopram and escitalopram are one of the main drugs belonging to SSRI class and appeared as a perfect example of evergreening.(26) First, escitalopram is the S-enantiomer of citalopram, the chiral compound. This is one of the reckoned methods of evergreening, also known as enantiomer patents.(27) Citalopram and escitalopram are produced by the same manufacturer. Citalopram is prescribed to 20 million patients worldwide, in over 70 countries. (24) While citalopram has expired in 2005, escitalopram was already approved by Food and Drug Association (FDA) in 2002. (28, 29) Lundbeck pharmaceutical has launched escitalopram as part of drug lifecycle management to extend the drug lifetime. On May 23, 2006, the FDA approved a generic version of citalopram by Teva. On July 14 of that year, however, the U.S. District Court of Delaware decided in favor of Lundbeck regarding the patent infringement dispute and ruled the patent on escitalopram valid.(30) In 2006 Forest Laboratories was granted an 828 day (2 years and 3 months) extension on its US patent for escitalopram. This pushed the patent expiry from December 7, 2009 to March 14, 2012.(31). Second, there is uncertainty in superiority of escitalopram over citalopram. There is a debate behind the general efficacy of antidepressant medication in literature questioning the effectiveness of the antidepressants.(32) The manufacturer of citalopram and escitalopram funded all available head-to-head trials, which emphasizes the risk of sponsorship bias and publication bias (suppression of trials with negative results).

2 Objectives

Our objectives were 1) to provide a general characterization of evergreening practices and, to evaluate the evergreening case study of citalopram/escitalopram, 2) to assess the relative efficacy between the revised version drug and the originated formula and 3) to assess health insurance reimbursement costs for the originated formula, its generic drugs and the revised version drug.

3 Methods

The project's objectives and methods were initially formalized in a study protocol, which was subsequently made available to the research department and the sponsor school.

3.1 Evergreening characterization

Firstly, we conducted a broad literature search to identify materials dedicated to evergreening. We looked for evergreening-related reviews, position papers or analyses published in medical literature, reports from national institutions, reports or articles from the pharmaceutical industry and articles dedicated to patent laws or case studies of patent-related lawsuits. We searched Medline (via Pubmed) and ScienceDirect, using free-text words for evergreening and its synonyms (stockpiling, drug lifecycle management, drug layering, patent line extension, me-too drugs and pay-for delay)[1]. We also searched Google and Google Scholar, looking in the results of the first five pages. Lastly, a reviewer manually searched the reference lists of all retrieved articles. A reviewer scanned through all identified reports and listed all couples of drugs described by primary authors as evergreened (i.e., the originated formula and the newly approved version of the drug).

Secondly, we characterized each identified couple of drugs. For both the originated formula and the newly approved version of the drug, we searched for active ingredient and trade names, commercializing pharmaceutical companies in Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) drug directory (Répertoire des Spécialités Pharmaceutiques Ecodex) and VIDAL drug compendium (33, 34). We looked for medical indications (in particular, whether the revised version targeted a specific population as compared to the originated formula, e.g. children or pregnant women) in AFSSAPS drug directory. We also searched the patent, marketing approval and commercialization dates using patent registries (French Patent Office Status Database, European Patent Register) and Legifrance Journal Officiel. We assessed the evergreening mechanism used: we looked for dosages, forms (tablets, pills, injections) and potentially modified release modes (e.g. extended release, orally disintegrated) in AFFSAPS drug directory and VIDAL compendium; we compared these characteristics between the originated formula and revised version and assessed the mechanism as chiral switching, formula change, release modification, different salts, different presentation, combination product or switch to the active metabolite. Lastly we looked for direct costs per unit in Assurance Maladie's drugs database (Base des médicaments et informations tarifaires BdM IT).

[1] For instance, the Pubmed search equation was evergreening OR ((stockpiling OR drug lifecycle management OR layering OR line extension OR me-too OR pay-for-delay) AND (drug OR pharmaceutical OR patent))

Finally, we selected evergreened drugs which would be further evaluated for efficacy assessment and cost burden estimates by applying the following selection criteria. The evergreened drugs should: (1) be produced by the same pharmaceutical company; (2) Be commercialized in the French market; (3) Have the same indication and targeting the same population sample; (4) Has never been repealed; (5) The patent expiry date of the originated drug and the approval date of the revised version should be around 2004 for reimbursement data availability reasons; (6) The different pairs of evergreened medications should represent different evergreening mechanisms

3.2 Assessment of relative efficacy between escitalopram and citalopram

To compare the efficacy of the originated formula citalopram and the revised version escitalopram, we performed a systematic review of randomized head-to-head trials, and we performed a meta-analysis of these head-to-head trials. Because of the different biases threatening this meta-analysis, especially sponsorship bias and publication bias, we also performed a systematic review of randomized trials comparing the originated formula or the revised version to placebo or another antidepressant agent, and we performed an indirect comparison of the evergreened drugs using mixed treatment comparison meta-analysis techniques.

An ongoing research project of the team found that identification of randomized trials evaluating second-generation antidepressant agents through an overview of reviews, instead of direct search for trials, has been successful. This method allowed identifying a larger number of trials than have been in published network meta-analyses in this field. For this reason, we adopted the same search strategy and looked first for reviews assessing citalopram or escitalopram efficacy.

3.2.1 Identification and selection of systematic reviews

Eligible reviews were assessing the efficacy of citalopram of escitalopram (any dosage form) in adults (18 years old or older) with major depression disorder via randomized controlled trials (whether head to head or involving one evergreened drug compared to other pharmacological treatments). Reviews which did not report efficacy assessment, interested in combination therapy, specific populations (e.g. patients with concomitant chronic medical condition) and those in other languages than English were excluded.

We searched for reviews published between January 2000 and March 2011 in the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), MEDLINE and EMBASE databases. The search equations were designed to reflect Participants (major depression and synonyms), Intervention (citalopram or escitalopram) and we used a filter to identify reviews in MEDLINE and EMBASE (see Appendix 3).

We also selected four reviews concerning antidepressant agents from national health technology agencies which were not indexed in bibliographical databases (one from the UK National Institute for Health and Clinical Excellence, one from the US Agency for Healthcare Research and Quality and two from the German Institute for Quality and Efficiency in Health Care).

3.2.2 Identification and selection of randomized controlled trials

Eligible trials were randomized double blinded trials; studying patients with major depression; comparing citalopram or escitalopram to placebo or another antidepressant agent; measuring a clinical outcome such as depression or functional status. Participants should have had an active intervention period of at least 4 weeks. Fixed-dosage and flexible dosage trials were eligible. Trials were identified through the screening of previously selected reviews.

We also searched for trial results reports from the FDA and Haute Autorité de la Santé (HAS) to uncover efficacy studies registered by regulators for approval and have not been published. For the latter, we searched the Drugs@FDA database which includes reviews for drug products approved since 1998; we screened systematically all medical and statistical reviews in Application Documents pertaining to citalopram or escitalopram. For the former, we searched the HAS web portal for assessment reports from the Comission de la Transparence, a committee which evaluates actual clinical benefit (in French, Service Médical Rendu) and improvement of clinical benefit (Amélioration du Service Médical Rendu) of drugs that are covered by National Health Insurance (NHI).

Lastly, we searched for trials results from the pharmaceutical companies commercializing citalopram/escitalopram through their trials results registries (www.lundbecktrials.com, www.forestclinicaltrials.com).

3.2.3 Data Extraction

The data extraction was performed by two reviewers independently. It was performed using a standardized form which was pilot-tested on five reports. Disagreements were resolved by discussion. For each trial report, the following data were extracted: first author's name; year of trial publication, publication status, drugs compared, outcome assessment delay, evaluated dosages (the range of administered dosages was abstracted for flexible dosage trials), numbers of randomized patients, numbers of analyzed patients, numbers of responders, means and standard deviations for baseline, follow-up depression scores and change from baseline to follow-up in scores, inclusion criteria age range, observed age distribution (mean, range), gender distribution and quality of safety data reporting.

3.2.4 Treatment effect measurement

We assessed acute treatment efficacy, which was defined as 8-week treatment. When the depression outcome was measured at several timepoints, we extracted outcome data at 8 weeks; if not reported, we extracted outcome data for the closest timepoints, ranging from 4 to 12 weeks.(35, 36)

Depression scores can be measured by different scales, the most common being Montgomery-Åsberg depression rating scale (MADRS), Hamilton Depression Rating (HAMD) scale or Clinical Global Impression. When results from several scales were reported, we extracted outcome data from MADRS; if not reported, we extracted data from HAMD scale.

Antidepressant trials commonly assessed efficacy using the change in depression score from baseline to follow-up (as a continuous outcome) or by using the proportion of patients with a decrease in depression score from baseline to follow-up of at least 50% (responders, as a binary outcome). In the first case, the treatment effect is measured using the difference between experimental and control groups in mean changes in depression scores (in meta-analysis of trials using different scales, a standardized mean difference is preferred). In the second case, the treatment effect is measured by the odds ratio or relative risk of response between experimental and control groups.

Because it was reported more frequently, we chose to perform the analyses on the dichotomous outcome rather than the continuous outcome. Consequently, efficacy was assessed through the proportion of responders in each treatment group. These proportions were derived on an intention-to-treat basis. The denominator was the total number of randomly assigned participants. Because deviations from the intention-to-treat principle were frequent, the numerator was the number of responders among the so-called efficacy subset (ie, patients who received at least one dose of drug and with at least one follow-up visit) and derived using the Last Observation Carried Forward method to handle drop-outs. Moreover, we assumed that randomized patients not included in the efficacy subset did not response to treatment (conservative approach).

When the numbers of responders were not reported, we used an imputation method based on the continuous outcome, i.e. mean baseline score and mean (standard deviation) of follow-up score or change in depression score from baseline to follow-up.(37, 38)

3.2.5 Meta-analysis of escitalopram vs. citalopram trials

A meta-analysis of head-to-head trials between escitalopram vs. citalopram was conducted. The effect of treatment was measured using odds ratios. Combined estimates were calculated using Mantel-Haenszel fixed-effect or random effects methods. Inconsistency of findings across trials was assessed using Cochran's Q statistic and the I^2 statistic with

associated 95% confidence interval (CI), the latter being the percentage of variability that is due to between-study heterogeneity rather than sampling error (chance): heterogeneity was classified as moderate ($I^2 \geq 30\%$), substantial ($I^2 \geq 50\%$) or considerable ($I^2 \geq 75\%$). In all cases, we considered the results from both fixed-effect and random effects models. For the latter, it is known that the estimate of the heterogeneity parameter is likely to be unreliable when the meta-analysis is based on a small number of studies. Hence, when the results from the trials were consistent, we preferred fixed-effect analysis.(39)

To address publication bias, we drew contour-enhanced funnel plots.(40) The effect estimate from each study was plotted against the inverse of the standard error. Because of sampling fluctuations, estimated effect sizes are more variable for smaller studies than for larger studies. Consequently, effect sizes scatter more widely at the base of the plot creating, in the absence of bias, a symmetrical funnel shape. If smaller, non-statistically significant studies tend to remain unpublished then an asymmetrical shape may be observed. Because publication bias is not the only possible cause of asymmetry, we superimposed contour lines indicating the conventional 0.05 level of statistical significance. If studies appear to be missing in areas of statistical non-significance, one is more confident in the possibility that the asymmetry is due to publication bias.

3.2.6 Indirect comparison meta-analyses

An adjusted indirect comparison was planned to estimate the relative efficacy of citalopram and escitalopram via the relative efficacy of each treatment compared to placebo. In fact, we suspected the head-to-head trials to be biased. As previously mentioned, we had knowledge of potential reporting bias since the pharmaceutical company recently rejected providing reports for three head-to-head trials. Moreover, we knew that all head-to-head trials had been sponsored by the pharmaceutical company, giving rise to a possible sponsorship bias. (41-43) However, adjusted indirect comparison would allow to estimate the comparison between escitalopram and citalopram and it may be less biased than direct comparison.(44)

The estimation method was described previously.(45) It consists in 1) estimating two combined log odds ratios, $\theta^{direct}_{ESC\ vs.placebo}$ and $\theta^{direct}_{CIT\ vs.placebo}$, via the meta-analyses of RCTs comparing escitalopram versus placebo and of RCTs comparing citalopram versus placebo and 2) to compute the difference in the log odds ratios $\theta^{indirect}_{ESC\ vs.CIT} = \theta^{direct}_{ESC\ vs.placebo} - \theta^{direct}_{CIT\ vs.placebo}$. The associated variance is estimated as $V\left(\theta^{indirect}_{ESC\ vs.CIT}\right) = \mathrm{Var}\left(\theta^{direct}_{ESC\ vs.placebo}\right) + \mathrm{Var}\left(\theta^{direct}_{CIT\ vs.placebo}\right)$. Confidence intervals and a chi-squared test statistic can be derived.

The primary indirect comparison meta-analysis was based on placebo-controlled trials. We also performed indirect comparison meta-analysis using other antidepressant agents as

common comparators, as long as trials comparing escitalopram to this drug and trials comparing citalopram to this same drug were available.

Sensitivity analyses were conducted by re-analyzing data after exclusion of trials without comparable dosages across arms, trials with imputation of outcome data, and trials which included elderly only. For the sensitivity analysis based on comparability of dosages, we assessed whether the dosage used in each trial arm corresponded to the defined daily dose (DDD) for antidepressant medications that has been settled by the WHO; we excluded trials as soon as a treated group received a dosage different from the DDD.

3.2.7 Mixed treatment comparison meta-analyses

To estimate the comparison between citalopram and escitalopram, we finally "borrowed strength" across all identified RCTs and we combined direct and indirect comparisons without breaking the randomization structure in the evidence.

Firstly, we did this using escitalopram-citalopram head-to-head trials together with placebo-controlled trials. Secondly, we did this using the whole network of RCTs, consisting of all existing trials comparing antidepressant agents with one another or vs. placebo. The network was represented by a graph in which nodes (or vertices) represent the competing treatments and lines connecting these nodes (or edges) represent the available RCTs. The diameter of nodes was proportional to the total number of patients who received the corresponding drug, and the width of edges was proportional to the number of trials addressing the corresponding comparison.

The combination of direct and indirect evidence (so-called mixed treatment comparison meta-analysis) was performed using the Bayesian hierarchical model of Lu and Ades.(46) A key assumption behind multiple-treatments meta-analysis is that the analyzed network is coherent— i.e., that direct and indirect evidence on the same comparisons do not disagree beyond chance. We assessed the consistency of the network by use of inconsistency factors.

All p-values were two-sided and $p < 0.05$ was deemed significant. Classical meta-analyses and indirect comparison meta-analyses were perfomed using Stata MP v10.0 (Stata Corp., College Station, TX) with the metan and metareg subroutines and Winbugs (Imperial College and MRC, v1.4.3, London, UK). Mixed treatment comparison meta-analyses were performed with WinBUGS v1.4.3 (Imperial College and Medical Research Council, 2004). The model was fitted by use of Bayesian inference computed with Monte Carlo Markov chain simulation. Convergence was assessed by using the Brooks-Gelman- Rubin diagnostic. After convergence was achieved from an initial 10,000 simulations (burn-in), we constructed posterior distributions of the effect sizes from 3 chains of 50,000 simulations.

3.3 Assessment of reimbursement costs for citalopram, its generic drugs and escitalopram

To assess the reimbursement burden for French general health insurance regimes related to escitalopram, still patent protected, and citalopram, which has generic drugs, we analysed data from the French national health insurance information system.

3.3.1 Assurance Maladie

Public health insurance program in France (known as the *Sécurité Sociale*) functions originally on professional activity.(47) It now includes several regimes. The main fund, Health Insurance Fund for Salaried Workers (Caisse Nationale d'Assurance Maladie des Travailleurs Salariés), covers eighty percent of the population. There are two additional funds for the self-employed and agricultural workers. Reimbursement is regulated through uniform rates. The financing is supported by employers, employee contributions, and personal income taxes. The working population has twenty percent of their gross salary deducted at source to fund the social security system. About seventy five percent of the total health expenditures are covered by the public health insurance system. A part of the balance is paid directly by the patients and the other part by private health insurance companies that are hired individually or in group (*assurance complémentaire or mutuelle*, complementary insurance or mutual fund). Complementary CMU facilitates access to health care for people with low income residing in France for more than three months, in a stable and uninterrupted manner. These individuals have one hundred percent coverage without advance payment for the health services or medication (they are fully covered, no money upfront needed). The income of the individual´s household must not exceed a maximum amount. The spouse or partner of the individual, as well as the dependents under 25 years of age is also included in this coverage. It is renewable on a yearly basis.(48)

3.3.2 Système National d'Informations Inter-Régimes de l'Assurance Maladie

In France, in the early 2000s, legislators ordered that the National Health Insurance regime develop *Système National d'Informations Inter-Régimes de l'Assurance Maladie* (SNIIR-AM) aimed at better understanding and evaluating beneficiaries' health care consumption and associated expenditures. In 2009, it contained data from the general health insurance regime that covers 86% of the French population; approximately 53 million people.

In addition, a permanent sample of Echantillon généraliste de bénéficiaires (EGB) was created from the SNIIR-AM database. This is a permanent, representative cross-sectional sample of the population covered by National Health Insurance which, since 2004, monitors beneficiaries' health care consumption over a period of 20 years. It contains anonymous

socio-demographic and medical characteristics and records of health care reimbursements. In 2009, it grouped together almost 500,000 beneficiaries covered by the National Health Insurance Fund for Salaried Workers; 77% of the population residing in France excluding public service employees and students. The EGB is used to conduct longitudinal studies as it permits tracing back patients' care paths and use of care in both hospital and office-based care environments and to calculate individual expenditures. It also permits the study of certain relatively frequent diseases characterized by a 100% reimbursement rate for certain chronic diseases and the reimbursement of tracer drugs. Eventually, the SNIIR-AM will include beneficiaries covered by all the different Health Insurance regimes in France.(49)

3.3.3 Data Extraction

We searched the database for the pair of evergreened drug using French identifiers for drug products Code Identifiant de Présentation (CIP code) for both the originated and the revised version formula drugs. The extraction has been performed using a SASguide syntax (appendix) designed to retrieve data concerning the basic reimbursement cost (a rate that is set by the Assurance Maladie on which the reimbursement cost percentage is based upon) .reimbursement amount paid by the Sécurité Sociale, prescription date and unique ID and CIPs' amount per prescription, consumer's year of birth and sex between Jan 2004 and Dec 2010, the data covered all existing CIPs. Each formatted request was performed on a group of 7 CIPs at a time, for the brand name of each drug and their generic form. The data were extracted into a text file format.

3.3.4 Analysis

The distinctive patients' number was extracted into a table to show the precise number and percentage of patients in the EGB population prescribed the evergreened medication and drug switch during the specified timeframe. Consumption frequency trends have been generated to illustrate the prescription consumption trend changes that are expected to occur when introducing the revised version of the originated formula. Time series plots have been produced to show the reimbursement costs change between the originated formula and the revised drug Formula, as well as the generic forms of Citalopram. Analysis on CIP codes was performed for the escitalopram and citalopram to illustrate the consumptions trend for certain forms of the medication. We further expressed consumption data in terms of defined daily doses (DDD) for antidepressant medications that has been set by the WHO (appendix 4). (50) The analysis was performed using Stata MP v10.0 (Stata Corp., College Station, TX).

4 Results

4.1 Evergreening characterization

Our literature search resulted in the identification of 24 couples of evergreened drugs. Table 1 summarizes the characteristics of these evergreened drugs. They covered a broad range of therapeutic indications (e.g., cardiovascular diseases, diabetes, allergy, psychological condition) with different purchasing conditions (e.g. with drug prescription or over the counter medication). Among the 24 identified cases, four were among the Leading Blockbuster Drugs List (namely, Lipitor, Seroplex, Nexium, Telfast)[2]. The identified evergreened medications were produced by 15 international pharmaceutical companies.

A wide range of evergreening mechanisms was covered; we covered complicated chemical modification like chiral switching to simple methods such as changing the drug dose, like in the case of glucophage 500mg and glucophage 1000 mg. Other evergreened mechanisms illustrate the fact of no gain of efficacy such as the case of Aricept (an Alzheimer disease medication produced by EISAI pharmaceutical, in which the revised version of the drug modified the form of release in the body from a normal tablet to an orally disintegrated tablet). In addition, the identified evergreening drugs spanned over a wide range of approval dates, 3 evergreened drugs revised versions were approved before 1990 , 4 couples were approved between 1990 and 2000 and 17 couples were approved between 2000 and 2010.

4.2 Assessment of relative efficacy between escitalopram and citalopram

4.2.1 Reviews identification and selection

Figure 2 presents the steps of the selection of reviews and the rationale of exclusions. We found 286 records through electronic literature (7 DARE, 1 Cochrane, 202 EMBASE, and 78 MEDLINE) and 4 reports were retrieved from health assessment agencies (National Institute for Health and Clinical Excellence, Agency for Healthcare Research and Quality and the German Institute for Quality and Efficiency in Health Care). Of these, 38 were duplicates and 190 were excluded on the basis of the title and abstract, leaving 58 full-text studies for further evaluation. Based on full-text articles, we finally selected 41 reviews fulfilling our inclusion criteria.

The reviews, mostly, did not focus specifically on citalopram or escitalopram but assessed generally antidepressants or the SSRIs drug class efficacy. There were 4 main reviews that

[2] http://www.reportbuyer.com/pharma_healthcare/prescription_drugs/blockbuster_drugs_2006_executive_overview.html
http://www.urchpublishing.com/publications/market_trends/pharmaceutical_market_trends_2010_2014.html

provided most of the randomized clinical trials: a Cochrane systematic review between escitalopram and other antidepressant agents (including citalopram); two network meta-analyses assessing the relative efficacy of antidepressants;(35, 41) a systematic review of FDA-registered placebo-controlled antidepressant trials.(51) The 41 reviews covered the whole period we searched (2000 to 2011) and consequently would allow to identify randomized trials over the whole range: 4 reviews were published between 2000 and 2002, 9 between 2003 and 2005, 13 between 2006 and 2008 and 15 between 2009 and 2011.

Figure 2: flow diagram of systematic reviews

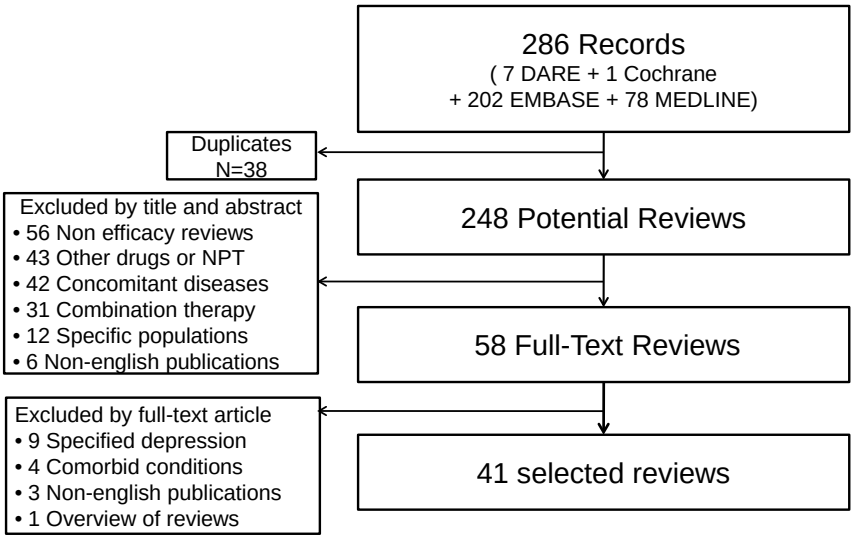


Table 1: characteristics of identified examples of evergreened drugs

	Originated formula					Revised version drug					
Company name	**Active ingredient**	**Trade name**	**Commer-cialization date**	**Date of approval**	**Repeal date**	**Active ingredient**	**Trade name**	**Commer-cialization date**	**Date of approval**	**Indication**	**Evergreening strategy**
Lundbeck	Citalopram	Seropram	22/01/1999	26/12/1994	Still valid	Escitalopram	Seroplex	18/05/2005	21/08/2002	Major depression	Chiral switching
UCBPharma	Cetirizine	Zyrtec	09/09/1998	04/12/1987	Still valid	Levocetirizine	Xyzall Change in form and dosage	11/04/2003	14/02/2002	Allergy	Chiral switching
Abbott	Clarithromycin	Zeclar	22/09/1999	11/09/1991	Still valid	Clarithromycine	Monozeclar	12/07/2005	11/08/2004	Antibiotic	Modified release & dosage
Astrazeneca	Oméprazole	Mopral,20 mg	25/09/1997	15/04/1987	Still valid	Esoméprazole	Inexium	20/03/2002	12/09/2000	Gastric ulcer	Chiral switching
Bristol - Myers Squibb	Pravastatine	Elisor	28/01/1995	10/08/1989	Still valid	Pravastatine +Aspirin	Pravadual	01/06/2006	24/10/2005	CV disease prevention	Combination products
GSK	Sumatriptan	Imigrane, 100 mg	15/08/1999	30/12/1994	11/08/2006	Sumatriptan succinate	Imigrane	26/06/1999	25/06/1998	Migraine attacks	Change in route of administration
Janssen Cilag	Econazole	Gyno pevaryl	13/09/1977	04/08/1976	15/04/2003	Econazole	Gyno pevaryl LP	11/11/1988	31/12/1987	Antifungal	Modified release
Janssen Cilag	Domperidone	Motilium	27/09/1986	10/03/1980	Still valid	Domperidone	Motilium	07/02/1996	28/11/1989	Antinausea	Form change
Laboratoires Fournier SA	Fenofibrate	Lipanthyl	21/02/1993	20/03/1990	Still valid	Fenofibrate	Lipanthyl	01/11/2001	09/10/2000	Lipid-lowering	Form change
Merck Sharp	Enalapril	Renitec	07/08/1994	22/03/1984	Still valid	Enalapril+ HCTZ	Corenitec	31/08/1988	29/12/1987	Hyper-tension	Combination products
Sanofi	Diltiazem	Ttildiem	11/11/1988	02/05/1979	Still valid	Diltiazem	Tildiem LP	22/03/1995	10/08/1990	Hyper-tension	Modified release
Sanofi	Alfuzosin	Xatral	31/08/1988	12/11/1987	Still valid	Alfuzosine	Xatral LP	26/03/1994	15/09/1993	Prostate adenoma	Modified release & dosage
Schering-Plough	Loratadine	Clarityne	31/08/1988	21/03/1988	Still valid	Desloratadine	Aerius	05/05/2002	15/01/2001	Allergies	Switch to the active metabolite

	Originated formula					Revised version drug					
Company name	**Active ingredient**	**Trade name**	**Commer-cialization date**	**Date of approval**	**Repeal date**	**Active ingredient**	**Trade name**	**Commer-cialization date**	**Date of approval**	**Indication**	**Evergreening strategy**
Servier	Indapamide	Fludex	07/01/1977	01/12/1986	Still valid	Indapamide	Fludex LP	12/04/2006	08/12/1994	Hyper-tension	Modified release & dosage
Servier	Gliclazide	Diamicron	08/11/2001	05/03/1998	Still valid	Gliclazide	Diamicron	20/10/2010	29/03/2000	Diabetes	Modified release
Lilly France	Fluxetine hydrochloride	Prozac Capsule	17/12/1994	01/04/1998	Still valid	Fluxetine hydrochloride	Prozac Tablet	20/10/2000	28/02/2001	Major depression	Chiral switching
Novartis	Methylphenidate hydrochloride	Ritaline	17/08/1996	31/07/1995	Still valid	Methylphenidate hydrochloride	Ritaline LP	25/06/2004	05/05/2003	ADHD	Modified release
Eisai	Donepenzil hydrochloride	Aricept	12/03/1998	03/09/1997	Still vlid	Donepezil hydrochloride	Aricept ODT	05/01/2007	22/02/2006	Alzheimer	Modified release
Sanofi	Glimepirid	Amarel	03/09/1997	14/11/1996	Still valid	Glimepirid	Amarel	NC	29/10/2003	Diabetes	Dosage modification
Pfizer	Atorvastatin calcium	Tahor	19/04/1998	21/03/1997	Still valid	Amlodipine besylate + atorvastatin calcium	Caduet	21/12/2006	07/07/2005	Lipid-lowering	Combination products
Astrazeneca	Zolmitriptan	Zomig	04/06/1998	28/08/1997	Still valid	Zolmitriptan	Zomingoro	07/07/2000	25/01/2000	Migraine attacks	Modified release
Servier	Indapamide	Fludex	07/01/1977	30/05/1973	Still valid	Perindopril + indapamide	Preterax bipreterax	13/08/2009	13/02/2007	Hyper-tension	Combination products
GSK	Ropinirole hydrochloride	Requip	08/05/2000	08/07/1996	Still valid	Ropinirole hydrochloride	Requip LP	10/01/2008	28/03/2007	Parkinson' s disease	Modified release
Merck Santé	Metformine	Glucophage	30/08/2000	21/03/1996	Still valid	Metformine	Glucophage	18/08/2001	10/01/2001	Diabetes	Dosage modification

CV: cardiovascular, HCTZ: Hydrochlorothiazide, ADHD: Attention deficit hyperactivity disorder

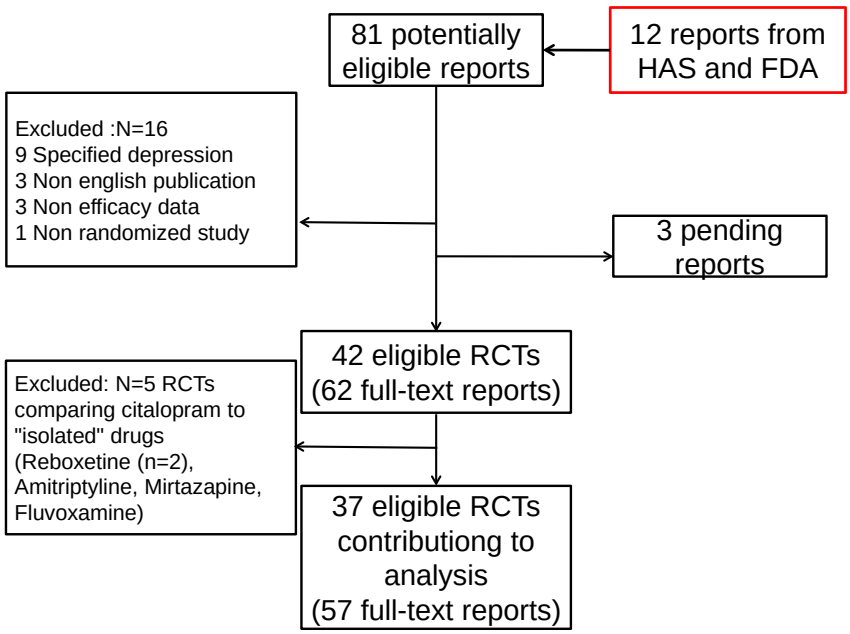
4.2.2 Randomized clinical trials identification and selection

Figure 3 summarizes the steps of the selection of randomized controlled trials assessing the efficacy of citalopram and/ or citalopram. From the 41 selected reviews, we retrieved 82 full-text reports concerning potentially eligible randomized clinical trials. This included 12 reports for escitalopram and citalopram drug approval from the FDA documents database or HAS Commission de la Transparence assessment reports.

After detailed screening of full-text reports and special care was given to link together related reports of a same trial, we selected 48 eligible RCTs (corresponding to 62 reports). The decision for reports of 3 RCTs is pending: data concerning these RCTs were found in an HAS report but they were not sufficient, we asked for data and information concerning those 3 RCTs to the HAS which has now offered support to query the pharmaceutical company.

Finally, 5 two-arm RCTs (corresponding to 5 reports) compared citalopram to "isolated" drugs (namely Reboxetine (n=2), Amitriptyline, Mirtazapine, Fluvoxamine) and thus were not contributing to the analysis. In other words, they were obviously not comparing citalopram to escitalopram, and because there was no trial comparing escitalopram to the same drugs, they could not contribute to an adjusted indirect comparison between citalopram and escitalopram. They were excluded.

Figure 3: flow diagram of randomized controlled trials selection



4.2.3 Description of selected trials

We selected 37 RCTs contributing to analysis (corresponding to 57 reports): 12 had published results only (13 reports), 7 had unpublished results only (2 reports from FDA and 5 reports from drug company) and 18 had both published and unpublished results (37 reports,

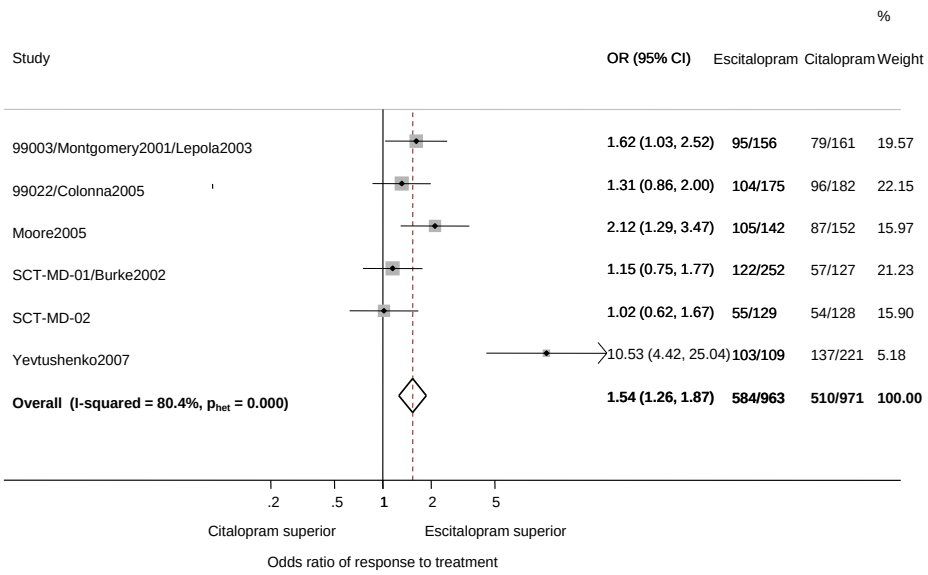
among which 7 from FDA). There were 27 two-arm RCTs and 10 three-arm RCTs, providing a total of 57 randomised comparisons: 6 head-to-head trials compared escitalopram to citalopram, 12 compared citalopram to placebo and 13 compared escitalopram to placebo; 31 RCTs compared escitalopram and/or citalopram to other antidepressants.

The included trials were covering a time period from 1992 to 2008 with a total of 12,840 participants. The number of patients per trial ranged from 67 to 684 (median 325). Outcome assessment timepoints ranged from 4 to 12 weeks, 1 study with 4-week measurement, 6 trials with 6-week measurement, 25 trials with 8-week measurement and 5 RCTs with 12-week measurement. The average depression score on MADRS scale at baseline ranged from 23.9 to 36.7 points (overall mean 30 points). The mean age per trial ranged from 35 years to 80 years (overall mean 45 years) The proportion of male patients per trial ranged from 20% to 68% (overall proportion 35%). Seventeen trials used fixed dosage and the remaining had flexible dosages regimen. Moreover, 13 trials were consistent with the defined daily dose recommendations.

4.2.4 Meta-analysis of escitalopram vs. citalopram trials

Figure 4 shows the meta-analysis of the 6 identified head-to-head trials comparing escitalopram to citalopram based on the probability of response to acute phase treatment. There was a statistically significant difference with escitalopram being more effective than citalopram (combined odds ratio 1.54, 95% CI 1.26 to 1.87, p = 0.006; 1934 participants).

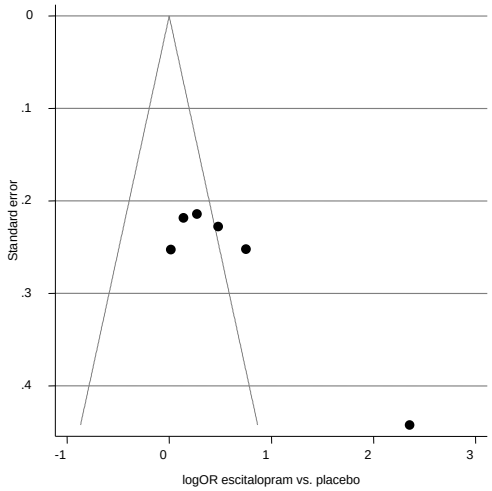
Figure 4 : meta-analysis of head-to-head trials comparing escitalopram to citalopram



Visual assessment of the funnel plot of the 6 trials did not reveal clear asymmetry (figure 5). Moreover, criteria to apply asymmetry tests were not met,, since we observed less than 10

trials and Yevtushenko 2007, a smaller trial with two combined citalopram dosage groups, showed outlying results leading to heterogeneity.

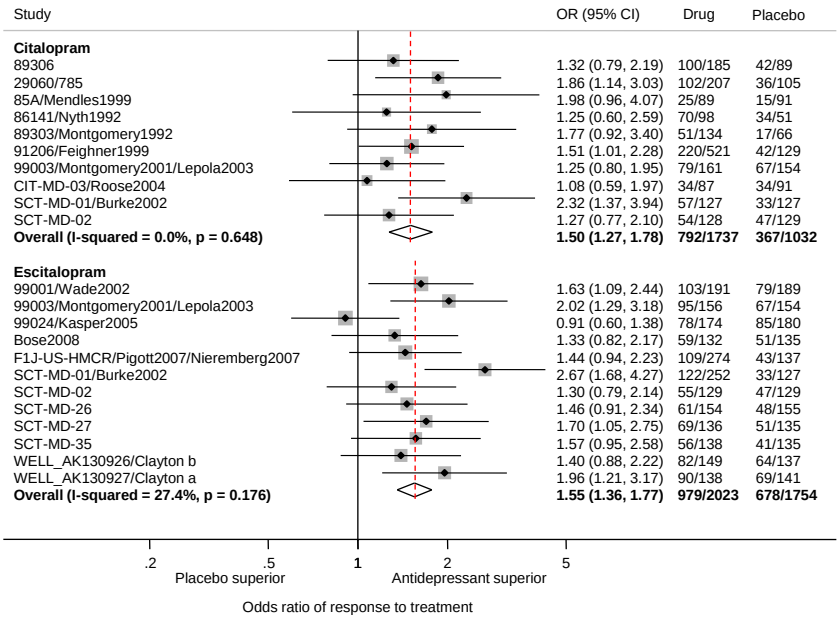
Figure 5 : funnel plot of head-to-head trials comparing escitalopram to citalopram



4.2.5 Indirect comparison meta-analyses

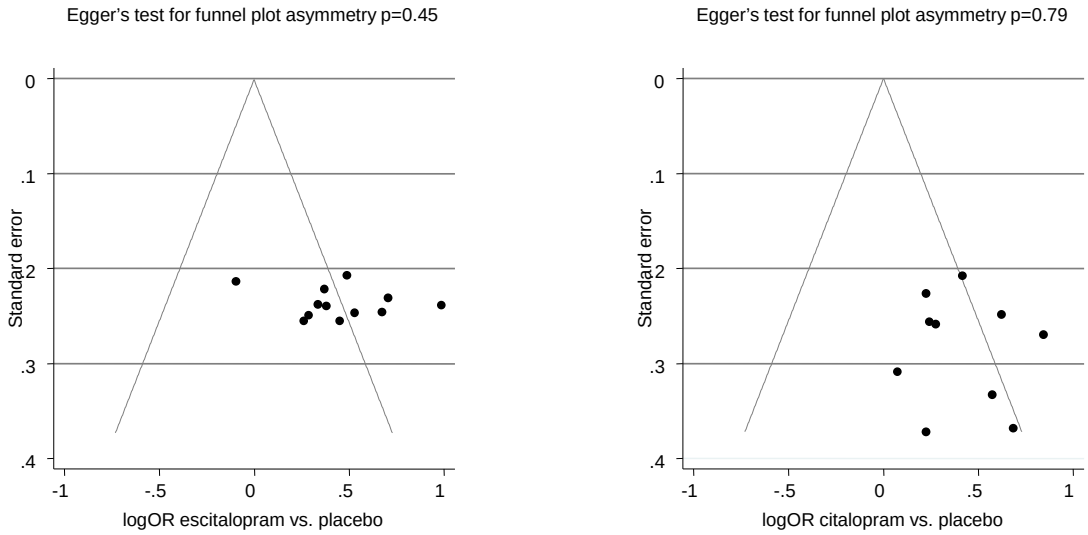
Figure 6 shows the 2 meta-analyses of the placebo-controlled trials for citalopram (n=10) and for escitalopram (n=12). It showed that citalopram and escitalopram were more effective than placebo and their effect sizes were similar: the combined odds ratio for citalopram vs. placebo was 1.50, 95% CI 1.27 to 1.78 and that for escitalopram vs. placebo was 1.55, 95%CI, 1.36 to 1.77. Consequently, the adjusted indirect comparison did not show any difference between citalopram and escitalopram (indirect odds ratio, 1.03, 95%CI, 0.83 to 1.28, p=0.79).

Figure 6 : meta-analyses of trials comparing escitalopram or citalopram to placebo



For each meta-analysis of placebo-controlled trials for citalopram and escitalopram, there was no evidence of publication bias based on visual analysis of the contour-enhanced funnel plots and statistical tests of funnel plot asymmetry (figure 7).

Figure 7 : funnel plots for of trials comparing escitalopram or citalopram to placebo



The 4 other indirect comparison meta-analyses, based on fluoxetine, sertraline, paroxetine or venlafaxine XR as common comparators did not show any difference between citalopram and escitalopram (see the Summary forest plot in the following subsection, figure 10). However, the numbers of trials were small.

Re-analyses of the direct comparisons and indirect comparisons after exclusion of trials without comparable dosages (25 trials overall), with imputed outcome data (14 trials overall) or which included elderly only (5 trials overall) showed consistent results with the primary analyses (Figure 8).

4.2.6 Mixed treatment comparison meta-analyses

In an attempt to borrow strength from all available RCTs, we performed two mixed-treatment comparison meta-analyses with the objective of estimating the contrast between citalopram and escitalopram. The first one was a weighted average of the direct evidence from head-to-head trials and the indirect evidence using placebo-controlled trials for citalopram and escitalopram. The second was a network meta-analysis, i.e. a method based on the overall synthesis of the entire network, combining direct comparison between the 2 antidepressant agents, first-order indirect evidence between the 2 antidepressant agents using placebo as common comparator and using other antidepressant agents as common comparators as well, second-order indirect evidence between the 2 antidepressant agents using pathways via duloxetine or bupropion (e.g., esc-bup-pla-cit or esc-dul-pla-cit) (figure 9).

Figure 8: sensitivity analyses based on the exclusion of trials without comparable dosages, with imputed outcome data, with elderly patients only

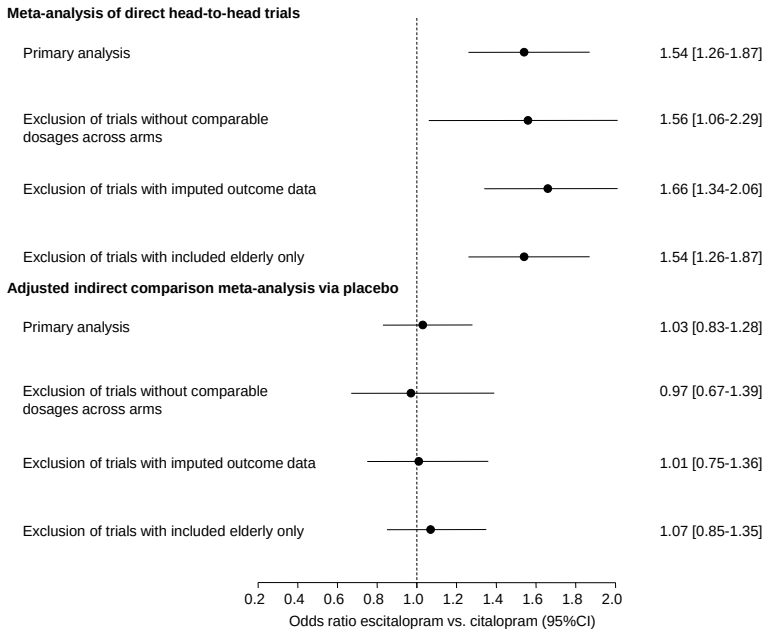


Figure 10 is a summary forest plot showing the results from all performed analyses. The results from the two mixed-treatment comparison meta-analyses are at the bottom and they are similar to that from the meta-analysis of direct head-to-head trials, with combined odds ratio for escitalopram vs. citalopram equal to 1.28, 95%CI, 1.11 to 1.48 for the weighted average of the direct indirect (via placebo) evidence and 1.31, 95%CI, 1.05 to 1.64.

However, the forest plot highlights the large discrepancies between indirect and direct evidence. This is also evidenced by the inconsistency factors in Table 2 which confirm that the indirect comparison meta-analyses yielded smaller treatment contrasts (with no evidence difference between citalopram and escitalopram) than the direct meta-analysis. These inconsistencies were always statistically significant.

Table 2: inconsistency factors between direct and indirect evidence

Closed loop via	Inconsistency factor (95%CI)
Placebo	0.40 (0.11 to 0.70)
Fluoxetine	0.32 (0.12 to 0.76)
Sertraline	0.41 (0.14 to 0.96)
Paroxetine	0.73 (0.20 to 1.27)
Venlafaxine XR	0.62 (0.03 to 1.21)

Inconsistency factors were computed as the difference in log OR between the meta-analysis of 6 head-to-head RCTs and each of the 5 adjusted indirect meta-analysis.

Figure 9: network of eligible comparisons for the network meta-analysis

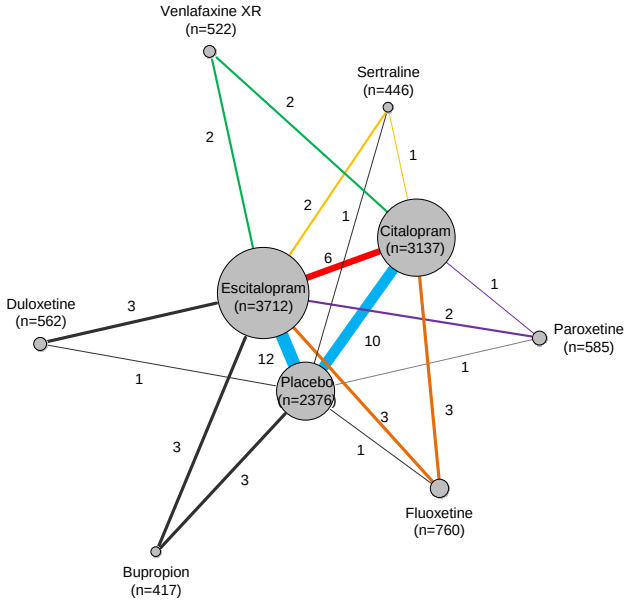
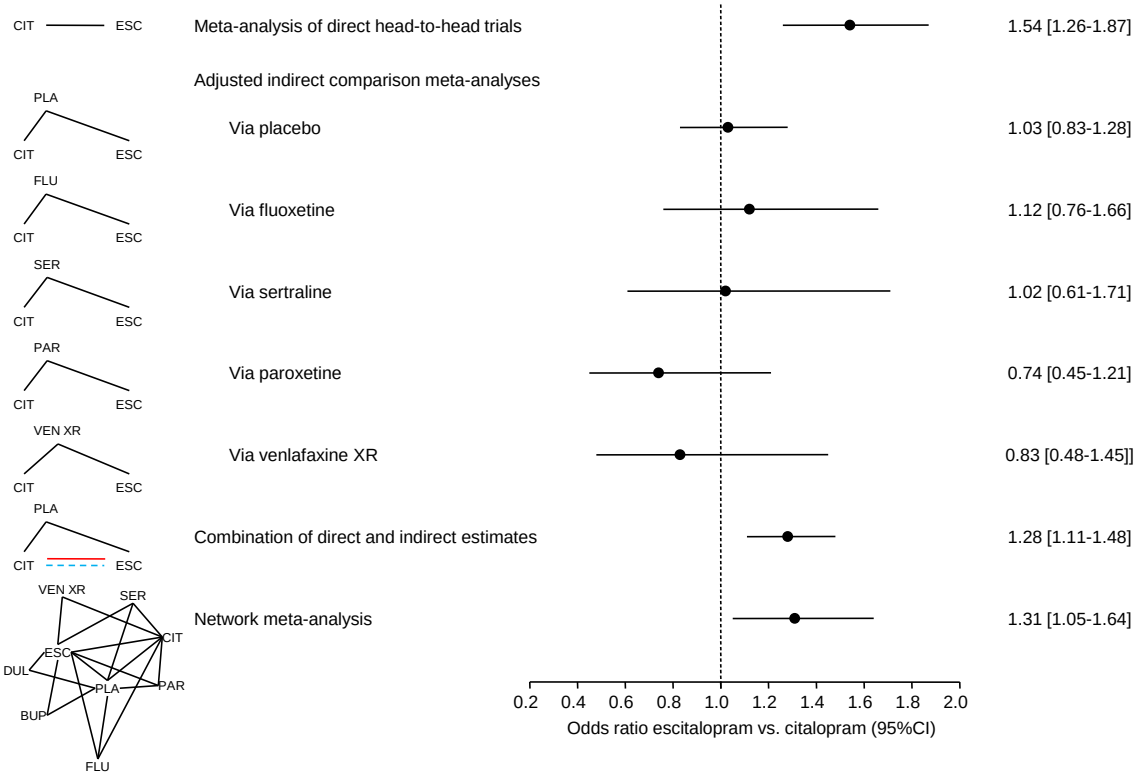


Figure 10: summary forest plot for the comparison between citalopram and escitalopram according to direct comparison, indirect comparison and mixed-treatment comparison meta-analyses



4.3 Assessment of reimbursement costs for citalopram, its generic drugs and escitalopram

4.3.1 Description of the cohort

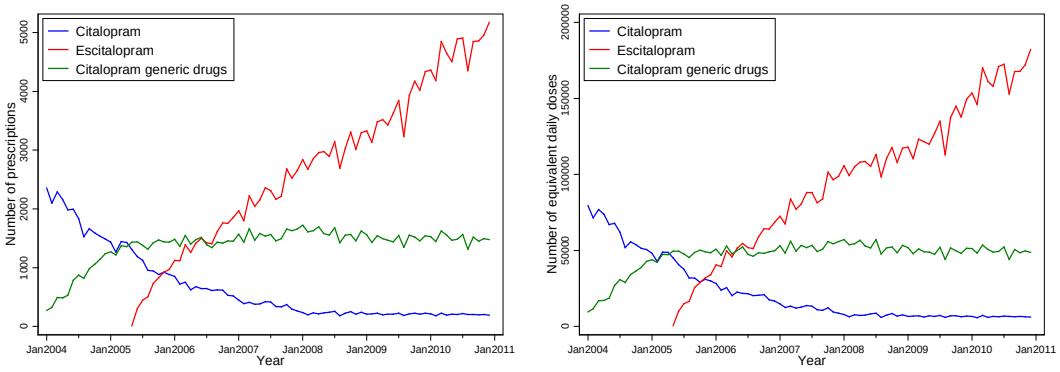
Our query of the SNIIR-AM EGB database resulted in reimbursements for 37,391 distinctive insurees (about 7% of the EGB sample) and a total of 358,355 reimbursements from 2004 to 2010. Their median age at the time of first reimbursement was 48 years [Q1-Q3: 37-62] and 69% were women. The median number of reimbursements per insuree was median 3 [Q1-Q3: 1-11], (range 1 – 172).

4.3.2 Consumption levels

Consumption levels were first examined by the distinctive numbers of patients purchasing the evergreened medication. The consumption of citalopram plummeted from 5793 patients in 2004 to 727 patients in 2010. With the introduction of escitalopram to the market in 2005, the revised formula rose from 1927 patients in 2005 to 11025 patients in 2010. The Generic form of citalopram was consumed by more patients in 2005 that in 2004 (3911 and 2861 respectively) (Figure 11).

The EGB sample showed a substantial decrease in the monthly consumption of citalopram between January 2004 and January 2006. Citalopram's consumption dropped down to less than third of what was consumed in 2004 (22,524 prescriptions). This decrease was faced by almost a double increase in the prescription purchased for the generic forms of citalopram in the same time period (8,999 in 2004 to 17,289 in 2006). In addition, the new revised formula escitalopram has taken 40% of the market share (17,620 prescriptions) in 2006 after it was introduced to the market in April 2005. Citalopram prescription trends continued to decrease in a lesser extent to reach 2,444 prescriptions in 2010. While the generic forms continued to rise to reach a peak of 19,089 prescriptions in 2008 and then decreased slightly to settle around 17,000 prescriptions in 2010. Escitalopram's prescriptions, however, grew dramatically to hit 56526 prescriptions by the end of 2010.

Figure 11: consumption levels (monthly numbers of prescriptions and DDDs)

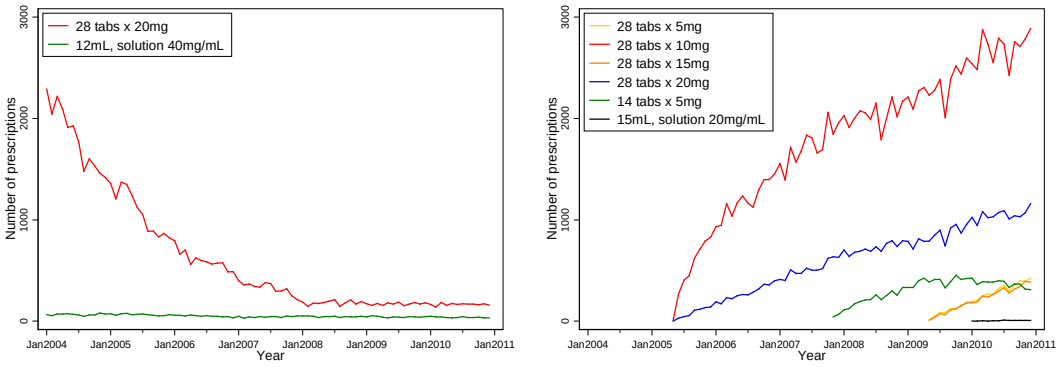


4.3.3 Consumption levels by CIP drug identifier

Citalopram has only two forms of the drug in the market, (28 tab x 20 mg/mL) and a 12 mL solution with a 40mg/mL concentration. The second form remained almost stable during the six surveyed years with low consumption levels. While the first form declined from more than 2,000 prescriptions in 2004 to slightly higher than the solution form in 2010.

One the other hand, escitalopram presented several CIPs in the market consumption. Two forms were first introduced into the market (28 tab x 10 mg/mL , 28 tab x 20 mg/mL) in April 2005 and they remained increasing during the period examined. A (14 tab x 5mg/mL) form appeared in the consumption trends in September 2007; other 28 tab CIPs one with a concentration of 5mg/mL and the second one with a concentration of 15 mg/mL followed the same trend after being introduced to the market in April 2009 (Figure 12).

Figure 12: consumption levels by CIP drug identifier



4.3.4 Numbers of Defined Daily Doses

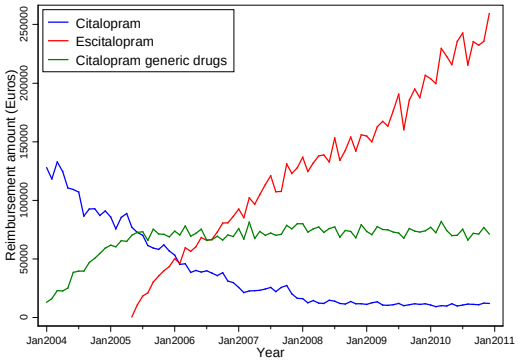
Drug consumption trends calculated in DDDs showed similar changes to those per prescription with citalopram dropping from 76,1912 DDDs in 2004 to 77,604 DDDs in 2010, compared to escitalopram DDD consumption which rocketed from 16,2190 in 2005 to 1,974,740 DDDs in 2010. The generic forms of citalopram managed to make some gains in

the market share in 2005 to reach 569,184 DDDs. However, this rise almost leveled off around 60,000 DDDs up to 2010 (Figure 11).

4.3.5 Reimbursement costs

On reimbursement aspects, total yearly costs dropped by around 40,0000 euros for citalopram from 2004 to 2005, while the generic form cost has risen to almost double the reimbursement cost from 2004 recording 82,1743 euros in 2005. At the same year, escitalopram costs 200,138 Euros. The cost burden of escitalopram continued to grow to reach 2727547 Euros in 2010, compared to the trade form of citalopram that reported a cost of 130996 Euros. The generic forms of citalopram had an almost constant cost level of less than 90,0000 euros for the years following 2005 till 2010 (Figure 13).

Figure 13: reimbursement costs



5 Discussion

The term “evergreening” usually implies perpetual renewal. It has now become the dedicated term to describe the various strategies to prevent competition after basic patent protection on a drug product has expired. In this three-part project, we were first able to characterize evergreening. We identified 24 couples of evergreened drugs. They covered a wide period, showing that this practice has long been known and is still used. They involved a variety of techniques to extend the duration of blockbuster medications’ patent for high prevalence diseases. We then focused on a case study of evergreening, the citalopram / escitalopram drugs. In a comparative effectiveness analysis, based on a large-scale systematic review of relevant RCTs, we found a large discrepancy between the direct and indirect efficacy comparison, where escitalopram was found superior to citalopram in the first comparison, while there was no evidence of difference in the indirect comparison. In a reimbursement costs analysis, based on an exploitation of the French National Health Insurance Health System, we found that the revised formula took a huge share of the market while the originated formula falls back giving part of the market share to the generic form. The

reimbursement and prescription analysis clearly illustrated the shift in consumption trends after the introduction of the revised version. The generic form of citalopram took a higher share than it used to do before the launch of the revised version (escitalopram). The CIP analysis showed the practice of launching different forms of the revised formula in different time periods. The reimbursement cost trends and amounts reflected the high reimbursement burden of escitalopram compared to citalopram and its generic form.

The substantial increase in the escitalopram consumption could be due to the aggressive marketing strategy adopted by Lundbeck pharmaceutical and sometimes breaking advertising rules (52).

Faced with our findings, one could ask whether direct comparison evidence should be prefered to the indirect evidence? Usually, head-to-head trials are considered the gold standard to evaluate the contrast in efficacy between two active treatments. Our findings are likely to be explained by underlying biases within the body of evidence of head-to-head trials comparing citalopram with escitalopram. Both drugs are produced by the same manufacturer and sponsorship bias could be at play (41-43). But the observed inconsistency may especially indicate reporting bias, with whole negative studies being suppressed. In fact, during our search process, we identified data from 3 large-size head-to-head trials reported in an HAS Commission de la Transparence review. Unfortunately, these data are not sufficient to be incorporated in our current analyses: the review only reports the observed difference between active drugs and placebo in mean changes from baseline to follow-up in depression scores. However, the data for the 3 RCTs show no evidence of difference between escitalopram and citalopram since the difference between escitalopram and placebo is consistently similar to the difference between citalopram and placebo (Table 3). Moreover, these data are not appearing in subsequent assessment reports from HAS concerning seroplex (e.g., AVIS du 19 mars 2008). We are in the process of querying the pharmaceutical company with support from HAS. A recent similar application for access to anti-obesity medication efficacy data from the pharmaceutical industry was successful with the help of the European Ombudsman.(53) In a soon-to-be-published update of AHRQ 2007 report concerning the comparative effectiveness of second generation antidepressants, Gartlehner and colleagues found similar results to ours when focusing on citalopram/escitalopram direct comparison.(35) In a more extensive mixed treatment comparison, taking the entire network of second-generation antidepressant RCTs into consideration, they even found a largely non significant superiority of citalopram over escitalopram with a wide credible confidence. Our mixed-treatment comparison meta-analyses and Gartlehener's should be interpreted cautiously. In fact, a required assumption for network meta-analysis is exchangeability (which implies that if all the RCTs had included

all the treatments evaluated in the network, then each trial would have estimated the same pairwise effect sizes). But unequal availability of trials for different comparisons, because of reporting bias, may lead to the violation of this consistency/exchangeability assumption.(54) In the end, given the likelihood of publication bias for head-to-head trials, the inherent limitation of the mixed treatment comparison meta-analysis, and the absence of evidence of reporting bias for placebo-controlled trials (a good of part of which are coming from the FDA which is considered as a gold standard from placebo-controlled trials in the antidepressant field),our adjusted indirect comparison may be less biased (44, 51, 55)

Table 3: Data from 3 RCTs reported in HAS Comission de la Transparence review concerning Seroplex (Ocotber 2004)

Study	Duration	N pat	Escitalopram vs placebo		Citalopram vs placebo	
99007	8 weeks	491	10mg:	MD -12.8	40mg:	MD -12.0
			20mg:	MD -13.9		
99008	8 weeks	375	10-20mg:	MD -12.9	20-40mg:	MD -13.0
99022	24 weeks	357	10mg: MD	MD -21.6	20mg:	MD -20.6

Our study has some limitations. Firstly, in the comparative effectiveness analysis, we did not assess safety outcomes. It would be important to compare the benefit/risk balance for the two drugs. However, different types of studies may be needed to evaluate different outcomes, observational studies are almost always necessary to assess harms adequately. (56) Thus a systematic review with broader selection criteria would be needed. Moreover, it is likely that safety data suffer, if not more than efficacy data, from reporting biases. Secondly, the fact that we examined the basic reimbursement cost without adding the complementary reimbursement amount may be another limitation. However, it is likely that the complementary reimbursement portion is small and would not affect the results of our analysis. Another limitation to our analysis might be the examination of the EGB database population sample which covers only about 1% of SNIIR-AM population. Albeit the EGB is a representative sample of the SNIIR-AM database and a survey methodology was used to sample for the EGB.

In conclusion, we analyzed case study representative of evergreening strategies: destroying enantiomer is not pure innovation and should theoretically not result in clinical benefit; nevertheless Lundbeck/Forrest maintained a form of monopoly with escitalopram. we found our data are supporting the supposed evergreening strategies: escitalopram may not bring benefit compared to citalopram since the discrepancy in direct and indirect efficacy comparison is likely explained by publication bias among head-to-head trials; escitalopram presence on the market (with a large market share) probably maintains delays in generics

introduction and prevents a substantial cost saving for health insurance. The methodology we described in this report, which combines secondary comparative effectiveness research through meta-analyses and exploitation of the very unique SNIIR-AM data, opens up the door for the assessment of other evergreened drugs.

6 References

1. Harding SK. Perpetual Property. Florida Law Review 2009(61):285

2. Organization WIP. What kind of protection does a patent offer? ; Available from: http://www.wipo.int/patentscope/en/patents_faq.html#protection.

3. Dwivedi G, Hallihosur S, Rangan L. Evergreening: A deceptive device in patent rights. Technology in Society. [doi: DOI: 10.1016/j.techsoc.2010.10.009]. 2010;32(4):324-30.

4. Wertheimer AI, Santella TM. Pharmacoevolution: the advantages of incremental innovation. International Policy Network2009.

5. Committee THoCH. The influence of the pharmaceutical industry 2006.

6. The National Institute for Health Care Management. Changing Patterns of Pharmaceutical Innovation. Washington D.C2002.

7. GlaxoSmithKline Pharmaceutical. Evergreening.

8. Fleming E, Ma P. Drug life-cycle technologies. Nat Rev Drug Discov. [10.1038/nrd926]. 2002;1(10):751-2.

9. Hughes DA, Ferner RE. New drugs for old: disinvestment and NICE. BMJ2010;340:c572.

10. Kubler P. New dugs for old. Australian Prescriber [Editorial]. 2006 December;29(Number 6):148-9.

11. Nair G. "Evergreening" an ever-green issue Pharma express2005 November.

12. Hiltzik M. Pharmaceutical industry defends 'pay-for-delay' deals2011: Available from: http://www.latimes.com/business/la-fi-hiltzik-20110511,0,1522323,print.column.

13. Bansal ISS, Deeptymaya Bakshi, Gautam Singh, Sukhjeet. Evergreening – A Controversial Issue in Pharma Milieu. Journal of Intellectual Property Rights2009;14:299-306.

14. Kumar S, Shukla N, Sangal T. Evergreening of Patents and Indian Patents Law. SSRN eLibrary2009.

15. Committee THoCH. The influence of the pharmaceutical industry

2004-2005;Vol. 1(Fourth report of the session).

16. Wyllie MG. Evergreening: there's life in the old drug yet. BJU Int2005 Jun;95(9):1359-60.

17. Thomas JR. Patent "Evergreening": Issues in Innovation and Competition In: Service CR, editor.2009.

18. Faunce T. The awful truth about evergreening. 2004; Available from: http://www.theage.com.au/articles/2004/08/06/1091732084185.html.

19. medicament Led. Propriété intellectuelle et médicament : une condition pour le progrès thérapeutique. 2006 [updated 03/05/2006]; Available from: http://www.leem.org/medicament/propriete-intellectuelle-et-medicament-une-condition-pour-le-progres-therapeutique-478.htm.

20. medicament Led. Circuit administratif du médicament. Paris2009; Available from: http://www.leem.org/medicament/circuit-administratif-du-medicament-417.htm.

21. Kondro W. Supreme Court rules against drug patent "evergreening". CMAJ2006 Dec 5;175(12):1508-9.

22. Zerjav S, Tse G, Scott MJW. Review of duloxetine and venlafaxine in depression. Canadian Pharmacists Journal2009;142(3):144-52.

23. Dolder C, Nelson M, Stump A. Pharmacological and clinical profile of newer antidepressants: Implications for the treatment of elderly patients. Drugs and Aging2010;27(8):625-40.

24. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med2006 Nov;3(11):e442.

25. Organisation for Economic Co-operation and Development Staff. Panorama de la santé 2009: Les indicateurs de l'OCDE2009.

26. Xavier Briffault YM, Philippe Guilbert, François Beck,. Évaluation de la dépression dans une enquête en population générale. Bulletin épidémiologique hebdomadaire2008(35-36).

27. Agranat I, Wainschtein SR. The strategy of enantiomer patents of drugs. Drug Discovery Today. [doi: DOI: 10.1016/j.drudis.2010.01.007]. 2010;15(5-6):163-70.

28. United State Patent and Trademark Office [database on the Internet]2011. Available from: http://www.uspto.gov/.

29. Lundbeck P. Annual report 2000: Lundbeck Pharmaceutical2000.

30. Miranda H. FDA OKs Generic Depression Drug. 2006; Available from: http://www.webmd.com/depression/news/20060523/fda-oks-generic-depression-drug.

31. Forest Laboratories I. Forest Laboratories Receives Patent Term Extension for Lexapro. 2007 [updated 2011]; Available from: http://www.frx.com/news/PressRelease.aspx?ID=824655.

32. Ioannidis JP. Effectiveness of antidepressants: an evidence myth constructed from a thousand randomized trials? Philosophy, Ethics, and Humanities in Medicine2008.

33. French drug registry [database on the Internet]. Available from: http://afssaps-prd.afssaps.fr/php/ecodex/extrait.php?specid=68446190.

34. French drug registry [database on the Internet]. Available from: http://vidal.ap-hop-paris.fr/html/recherche/recherche_produit?_application=vcim&_content=html&_dataClass=recherche&_name=recherche_produit.

35. Gartlehner G, Gaynes BN, Hansen RA, Thieda P, DeVeaugh-Geiss A, Krebs EE, et al. Comparative benefits and harms of second-generation antidepressants: background paper for the American College of Physicians. Ann Intern Med2008 Nov 18;149(10):734-50.

36. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet2009 Feb 28;373(9665):746-58.

37. Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. J Clin Epidemiol2006 Jan;59(1):7-10.

38. Furukawa TA, Cipriani A, Barbui C, Brambilla P, Watanabe N. Imputing response rates from means and standard deviations in meta-analyses. Int Clin Psychopharmacol2005 Jan;20(1):49-52.

39. Whitehead A. Meta-Analysis Of Controlled Clinical Trials. Front Matter2003:i-xiv.

40. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol2008 Oct;61(10):991-6.

41. Cipriani A, Santilli C, Furukawa TA, Signoretti A, Nakagawa A, McGuire H, et al. Escitalopram versus other antidepressive agents for depression. Cochrane Database Syst Rev2009(2):CD006532.

42. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. JAMA2003 Jan 22-29;289(4):454-65.

43. Djulbegovic B, Lacevic M, Cantor A, Fields KK, Bennett CL, Adams JR, et al. The uncertainty principle and industry-sponsored research. Lancet2000 Aug 19;356(9230):635-8.

44. Song F Fau - Harvey I, Harvey I Fau - Lilford R, Lilford R. Adjusted indirect comparison may be less biased than direct comparison for evaluating new pharmaceutical interventions. (0895-4356 (Print)).

45. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol1997 Jun;50(6):683-91.

46. Lu G, Ades AE, Sutton AJ, Cooper NJ, Briggs AH, Caldwell DM. Meta-analysis of mixed treatment comparisons at multiple follow-up times. Stat Med2007 Sep 10;26(20):3681-99.

47. Sociale S. home page. 2011; Available from: http://www.securite-sociale.fr/.

48. Stephanie Brunner. The French Health Care System. 2004 [updated 8 June 200908 Jun 2009]; Available from: http://www.medicalnewstoday.com/articles/9994.php.

49. Tuppin P, de Roquefeuil L, Weill A, Ricordeau P, Merlière Y. French national health insurance information system and the permanent beneficiaries sample. Revue d'Épidémiologie et de Santé Publique. [doi: DOI: 10.1016/j.respe.2010.04.005]. 2010;58(4):286-90.

50. WHO Collaborating Centre for Drug statistics Methodology, Norwegian Institute of Public Health. ATC/DDD Index 2011. 2011 [updated 2010-12-21]; Available from: http://www.whocc.no/atc_ddd_index/.

51. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med2008 Jan 17;358(3):252-60.

52. Dyer O. Lundbeck broke advertising rules. BMJ2003 May 10;326(7397):1004.

53. Gotzsche PC, Jorgensen AW. Opening up data at the European Medicines Agency. BMJ;342:d2686.

54. Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. Stat Methods Med Res2008 Jun;17(3):279-301.

55. Moreno SG, Sutton AJ, Turner EH, Abrams KR, Cooper NJ, Palmer TM, et al. Novel methods to deal with publication biases: secondary analysis of antidepressant trials in the FDA trial registry database and related journal publications. BMJ2009;339:b2981.

56. Chou R, Aronson N, Atkins D, Ismaila AS, Santaguida P, Smith DH, et al. AHRQ series paper 4: assessing harms when comparing medical interventions: AHRQ and the effective health-care program. J Clin Epidemiol May;63(5):502-12.

7 Appendix

Figure 14: depression phases

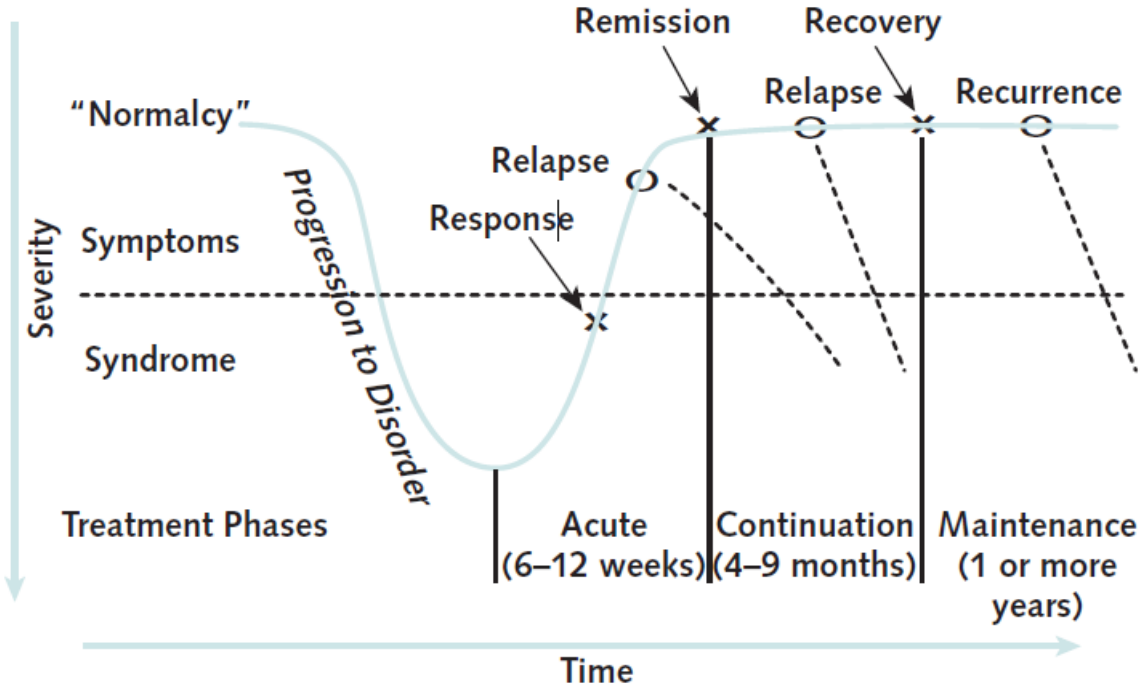


Table 4: search equation for Cochrane Database for Systematic Reviews

"major depression" OR "major depressive" OR "citalopram" OR " seropram" OR "seroplex" OR "escitalopram" in Title, Abstract, Keywords
Results: Cochrane Reviews [32] Other Reviews [54]

Table 5: search equation for Medline

Participants:	#1 ("Depressive Disorder"[Mesh] OR "Depressive Disorder, Major "[Mesh] OR "major depression"[Text Word] OR "major depressive disorder"[Text Word])
Intervention	#2 ("Citalopram"[Mesh] OR "citalopram"[Text Word] OR "desmethylcitalopram"[Text Word] OR "seropram"[Text Word] OR "seroplex"[Text Word] OR "cipramil"[Text Word] OR "celexa"[Text Word] OR "Lexapro"[Text Word] OR "cipralex"[Text Word])
Review Filter	#3 ("systematic"[sb])
Equation	#1 AND #2 AND #3
Results: 78	

Table 6: search equation for Embase

Participants	#1 'major depression'/exp OR 'major depression' OR 'major depressive'

Intervention	#2 'citalopram'/exp OR 'escitalopram'/exp OR citalopram OR escitalopram OR seropram OR seroplex OR cipramil OR celexa OR lexapro OR cipralex OR lexamil OR lexam
Type of study	#3 'meta-analysis':ti OR 'meta-analysis':ab OR 'meta-analysis':de OR 'search':ti OR 'search':ab OR 'review':pt
Equation	#1 AND #2 AND #3
Results	315

Table 7: list of CIP codes and their dosages and DDD equivalence

CIP	Dose	NB of mg/ml	DDD	NB of mg/mL × DDD
Citalopram				
3383361	20	28	1	28
5705107	20	98	1	98
5607563	20	100	1	100
5615580	40	5	2	10
3465372	40	12	2	24
5615597	40	10	2	20
Escitalopram	**Dose**	**NB of mg/ml**	**DDD**	**NB of mg/mL × DDD**
5637067	5	100	0,5	50
3599374	10	28	1	28
5637073	10	100	1	100
5709513	10	98	1	98
3599397	15	28	1,5	42
5709536	15	98	1,5	147
3599411	20	28	2	56
5637104	20	100	2	200
5709542	20	98	2	196
3820459	20	15	2	30
5745041	20	75	2	150
3599351	5	28	0,5	14
3642897	5	14	0,5	7
5709507	5	98	0,5	49
Citalopram generic drugs	**Dose**	**NB of mg/ml**	**DDD**	**NB of mg/mL × DDD**
3737534	20	28	1	28

3647713	20	28	1	28
3899768	20	28	1	28
3667727	20	28	1	28
3667733	20	30	1	30
3605904	20	28	1	28
5640419	20	100	1	100
3665088	20	28	1	28
3667762	20	28	1	28
4197988	20	28	1	28
3639464	20	28	1	28
5651765	20	100	1	100
3647245	20	28	1	28
3639406	20	28	1	28
3616776	20	28	1	28
3616813	20	28	1	28
3846163	20	28	1	28
3639352	20	28	1	28
3648463	20	28	1	28
3656066	20	28	1	28
3688770	20	28	1	28
3674325	20	28	1	28
3881716	20	28	1	28

Figure 15 : consumption levels (monthly numbers of prescriptions and DDDs)

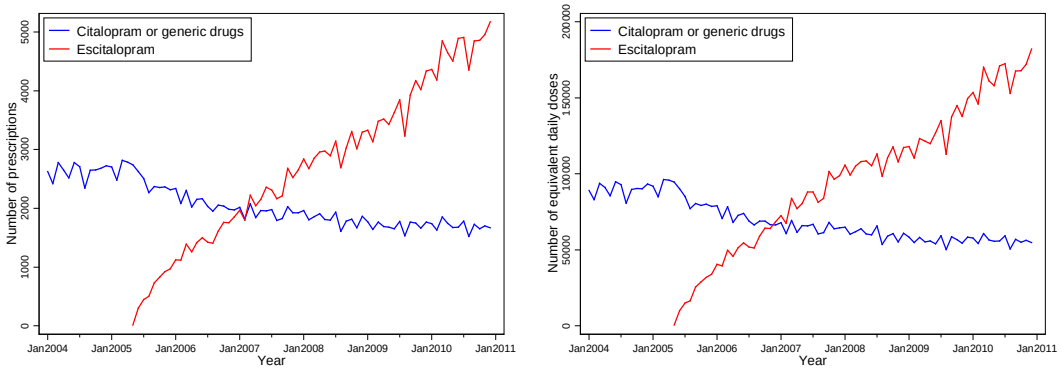


Figure 16 : reimbursement costs