The use of network meta-analysis in the economic evaluation of the cost – effectiveness ratios of treatments

استخدام شبكة التحليل الشامل في التقييم الاقتصادي لنسب التكلفة والفعالية للعلاجات

Ahmed Hamimes [1]
National Higher School Of Statistics And Applied Economics, Tipaza (Algeria),
ahmedhamimes@yahoo.com

Rachid Benamirouche
National Higher School Of Statistics And Applied Economics, Tipaza (Algeria),
rbena2002@hotmail.com

Received: 25/09/2020 Accepted: 16/11/2020 Published: 30/06/2021

Abstract

Given the insufficient clinical investigation to understand the protection mechanisms, the public authorities are seeking to optimize health spending with better quality drugs on the Algerian market. The globalization of biomedical research provided systematic information, we need a tool like meta analysis which will allow us to synthesize and adapt this knowledge in our health system. Meta analysis is the systematic approach summarizing the conclusions of a collection of studies conducted independently on a specific research problem, in many medical specialties. Using different meta-analysis techniques it is possible to classify the products according to their effectiveness and assess the cost – effectiveness ratio. In this article, we use the Bayesian approach in the context of multi-processing meta-analysis, we essentially rely on Gibbs sampling to solve the posterior distributions. We are studying the important role of integrating the tools for synthesizing published trials via the multi-treatment meta-analysis into three treatments plus placebo for people with bipolar disorder.

Keywords: Meta-analysis, multi-treatment meta-analysis, bipolar disorder.

JEL classification : C11, C15, J28, J38, L15.

ملخص

نظرًا لعدم كفاية التحقيقات السريرية (محدودية اختبارات المرحلة الرابعة للتجارب السريرية) لفهم آليات الحماية داخل المجتمع، تسعى السلطات العمومية إلى تحسين الإنفاق الصحي وهذا وفق أفضل جودة للأدوية في السوق الوطني. نظرًا لأن عولمة البحث الطبي الحيوي توفر المعلومات في شكل منهجي، فنحن بحاجة إلى أداة مثل التحليل البعدي الذي سيسمح لنا بتجميع هذه المعرفة وتكييفها في نظامنا الصحي وبالتالي الاستغناء عن هذه التحقيقات السريرية وتكاليفها العالية. التحليل الشامل هو نهج يلخص نتائج مجموعة من الدراسات التي أجريت بشكل مستقل حول مشكلة بحثية محددة، عبر العديد من التخصصات الطبية.

[1] **Corresponding author**.

باستخدام تقنيات مختلفة، من الممكن تصنيف المنتجات وفقًا للفعالية وتقييم نسبة التكلفة والفعالية. في هذه المقالة، نستخدم النهج البايزي " Bayesian " في إطار التحليل الشبكي الشامل ، ونعتمد بشكل أساسي على أخذ عينات Gibbs لحل التوزيعات اللاحقة. يتم التحقق من الدور المهم لأدوات التجميع التجريبية للمعلومات المنشورة من خلال التحليل الشبكي الشامل وهذا من خلال دراسة تشمل ثلاثة علاجات بالإضافة إلى العلاج الوهمي للأشخاص الذين يعانون من اضطراب ثنائي القطب.

الكلمات المفتاحية: تحليل شامل، تحليل شبكي شامل، اضطراب ثنائي القطب.

تصنيف JEL : C11,C15 ، J28 ، J38 ،L1

Introduction

The health of the population of a country and its economic development go hand in hand, where the relationship with health requires the rationalization of available resources, in particular financial and human resources. When health spending represents 4.9% of Algerian GDP despite the fact that its health system is in crisis, we understand that this rationality must be seen as a mechanism supported by therapeutic efficacy, where we must read medical information. in the hierarchy of the health system, and through this dynamism.

Clinical trials were previously administered only in industrialized countries where the economic, health and social conditions encountered in developing and emerging countries often complicate the performance of extensive clinical trials, they are now with the globalization of biomedical research administered in countries industrialized and also in developing countries, on the other hand, other countries have not created an industrial fabric of pharmaceutical production supported by local clinical research, these being affected by the insufficiency of the means necessary to carry out examinations and procedures, or for reasons related to the economic policies of the state, but when the knowledge is found in several laboratories and clinical investigation centers (CICs) in several countries, we would like a tool like meta-analysis which can allow us to synthesize the use and adapt this data in our health system, where the meta-analysis is that the systematic approach summarizing the conclusions of a set of studies administered independently on a selected research problem, in many medical specialties.

This work is an attempt to carry out a multiprocessing meta-analysis in a Bayesian framework, in order to answer the following problem:

"**Given the insufficiency of clinical investigations to understand the mechanisms of drug protection, what is the ideal tool by which public authorities can improve health spending with better quality of medicines on the Algerian market?"**

Economic valuation has become an increasingly valuable decision-making method in recent years to help resolve resource allocation issues. Economic testing of healthcare approaches is primarily based on prospective randomized clinical trials (RCTs) (Adams M.E, McCall N.T, Gray

D.T et al, 1992), but there has been no difficulty in combining economic evaluations and clinical trials (Drummond, M. F., & Davies, L. , 1991). In some cases, the forward-looking design may not be feasible, acceptable or necessary for the purposes of economic analysis. As a result, a good proportion of economic evaluations rely on models that synthesize data from various research studies, expert opinion, current literature, and databases to varying degrees. Some researchers have suggested that modeling is an inevitable fact of existence ((Buxton M.J, Drummond M.F, van Hout B.A, Prince R.L, Sheldon T.A, Szucs T, Vray M, 1997)), but others have argued that the limits should be implicitly known to analysts (Sheldon T.A, 1996). A family of statistical strategies for integrating the results of related studies is given by meta-analysis.

In this article we use this approach in the framework of multitraitement meta-analysis, we mainly rely on Gibbs sampling as a tool for solving complex posterior equations. The important role of integrating published trial synthesis tools through multi-treatment meta-analysis in three treatments plus placebo for people with bipolar disorder (see Appendix) is being explored. The Bayesian approach was first described and is the most frequently used in meta-analysis methods ((Higgins, J. P. and A. Whitehead, 1996); (Whitehead, A, 2002); (Lu, G. and A. E. Ades, 2004)). This approach and within this framework is based on the calculation of the posterior distributions of the set of parameters on the stochastic algorithm MCMC (Gibbs sampling algorithm).

1. Bayesian statistics

Bayesian statistics have undergone significant progress over the past thirty years, with the development of computational methods and iterative algorithms with Markovian properties that make it possible to overcome complexity obstacles. The concept of Bayes differs from the classical concept whose meaning where the parameter is a random variable whose behavior is supposed to be known, by associating it with a probability distribution on the space Θ called a priori distribution and denoted $\pi\ (\theta)$ describes what 'we know and what we do not know before the observation X, through this design the statistical analysis allows to consider all the qualitative and quantitative information on the uncertainty in the model. Then, if we use Bayes' rule which allows to reverse the probabilities, we can deduce the a posteriori distribution $\pi\ (\theta\ /\ x)$ which allows us to construct inferential procedures in the most natural way possible, which also explains the persistence of this paradigm, against all odds for 250 years. Bayesian statistical analysis makes it possible to combine several sources of information on uncertainty in the model, also it provides results of interpretation that are more direct (less complicated) and richer than those of classical statistics, this approach respects the principle likelihood which means that all the information from a data set is contained in the likelihood function.

A posteriori distribution is defined by

$$\pi(\theta/x) = \frac{f(x/\theta) \times \pi(\theta)}{\int_{\Theta} f(x/\theta) \times \pi(\theta) d\theta} = \frac{f(x/\theta) \times \pi(\theta)}{m(x)} \qquad (1)$$

This a posteriori distribution is the combination of:

- $f(x/\theta)$ the density function of x knowing the value of the random variable θ.
- $\pi(\theta)$ models the density function a priori on θ.
- $m(x)$ the marginal distribution of x.

Expression (1) represents what is known about the parameter considering the observed data; it is also the update of $\pi\ (\theta)$ after observing our sample.

Once we have the data, the quantity $m\ (x)$ is a normalization constant which guarantees that $\pi\ (\theta\ /\ x)$ is indeed a probability distribution. We can write :

$$\pi(\theta/x) \propto f(x/\theta) \times \pi(\theta) \qquad (2)$$

Expression (2) shows that Bayesian inference satisfies the likelihood principle: a posteriori, the information from the data comes exclusively from the likelihood $f\ (x\ /\ \theta)$ (Begin, J .F, 2010).

An estimator $\delta^*(x)$ is a Bayes estimator under the cost $L(\theta, \delta)$ if it minimizes the Bayesian risk i.e .:

$$\delta^* = arg \min_{\delta} \int_{\Theta} \int_{\chi} L\left(\theta, \delta(x)\right) f(x/\theta)\pi(\theta) dx\, d\theta \qquad (3)$$

For the cost L^2 (the quadratic loss) defined by $L(\theta, \delta) = (\theta - \delta)^2$, the expectation of the posterior distribution is a Bayes estimator:

$$\hat{\theta} = E(\theta/X) = \int_{\Theta} \theta\, \pi(\theta/x)\, d\theta = \frac{\int_{\Theta} \theta f(x/\theta) \times \pi(\theta) d\theta}{\int_{\Theta} f(x/\theta) \times \pi(\theta) d\theta} \qquad (4)$$

If no specific loss function is available, estimator (4) is often used as a default estimator, although alternative solutions are also available. For example, The posterior maximum estimator (the posterior mode) defined by:

$$\hat{\theta} = arg \max_{\theta} \pi(\theta/x) = arg \max_{\theta} f(x/\theta)\pi(\theta) \qquad (5)$$

We can calculate the posterior distribution directly in the simple case or we do the calculation by MCMC simulation in the case where the calculation of the integral is very complex.

2. The Bayesian approach to meta-analysis

2.1. The random-effects and fixed-effects meta-analysis model

We pose:

δ :The observed effect of the treatment, traitement, the true effect of the treatment,

ξ^2: The inter-trials variance τ^2: the intra (between) -trialsvariance.

μ_i: The mean of the event rate of trial i in the logit scale.

The model of Smith, Spiegelhalter and Thomas was developed for binary data, on trials comparing two types of treatments: T (treatment) and C (control). The principle is to model the number of successes in the test (noted r_i) by a binomial distribution of parameters (n_i; p_i) (respectively number of patients and probability of success in test i; with by exponent T or C according to whether it is the experimental or control arm):

$$r_i^T \sim bin(p_i^T, n_i^T)$$
$$r_i^c \sim bin(p_i^c, n_i^c)$$

We then pose :

$$logit(p_i^T) = \mu_i + \delta_i/2$$
$$logit(p_i^c) = \mu_i - \delta_i/2$$

Where

$$\delta_i = logit(p_i^T) - logit(p_i^C) = logOR_i^{TC}$$

LogOR approximately follow a normal distribution. We can therefore write that these δ_i follow a normal distribution centered on the true difference Θ of the effect of the T and C treatments in the logit scale.

The fixed effects model is given by:

$$\delta_i = \Theta + \varepsilon_i$$

In a fixed-effects model, the true treatment effect is the same for all studies.

$$\delta_i \sim \mathcal{N}(\Theta; \tau_i^2)$$

We pose

$$\varepsilon_i \sim \mathcal{N}(0; \tau_i^2)$$
$$\delta = \sum_{i=1}^{r} \omega_i \delta_i \Big/ \sum_{i=1}^{r} \omega_i$$
$$Se(\delta) = \sqrt{1 \Big/ \sum_{i=1}^{r} \omega_i}$$
$$\omega_i = 1/\tau_i^2$$

We make the previous model more complex so as not to have to make the assumption of homogeneity of the effect by injecting a random effect.

In a random effects model, the structural assumption assumes that the true effect of each study is sampled according to the normal distribution: $\delta_i \sim \mathcal{N}\left(\Theta; \tau_i^2 + \xi^2\right)$

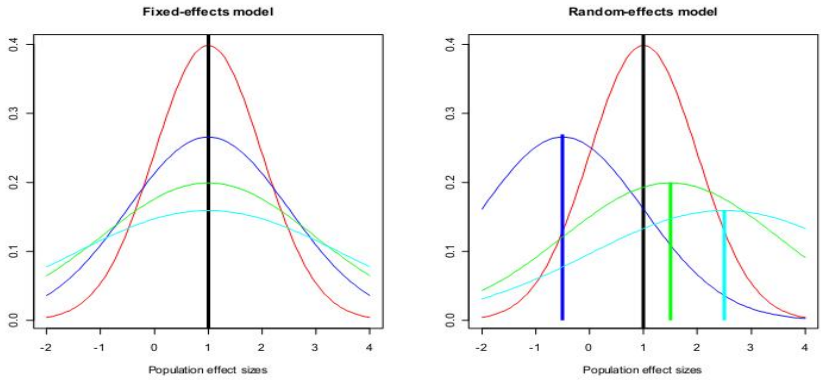
We pose

$$\varepsilon_i \sim \mathcal{N}\left(0; \tau_i^2\right)$$
$$\vartheta_i \sim \mathcal{N}\left(0; \xi^2\right)$$

The random effects model is

$$\delta_i = \Theta + \vartheta_i + \varepsilon_i$$
$$\delta^* = \frac{\sum_{i=1}^{r} \omega_i^* \delta_i}{\sum_{i=1}^{r} \omega_i^*}$$
$$Se(\delta) = \sqrt{\frac{1}{\sum_{i=1}^{r} \omega_i^*}};\ \omega_i^* = 1/\left(\omega_i^{-1} + \tau_i^2\right)$$

Figure 1. The representation of fixed and random effects models.



Source: Produced by the authors.

2.2. the "MTC" multi-treatment meta-analysis

Network[2] meta-analysis (multi-treatment) is a relatively new approach that combines direct and indirect[3] comparisons of the effects of treatments. The meta-analysis of multiple treatments with several objectives (Quilici, S, 2012):

- compare several treatment options simultaneously;
- perform a single analysis;
- the assessment of the validity of the results provided by the adjusted indirect comparison;

[2] In English, "network meta-analysis, multiple-treatment meta-analysis, mixed treatment comparison meta-analysis".

[3] In the case of a closed network, all the treatments were compared directly.

• the results of the indirect method confirm or refute the results of the direct comparison method;

• determine which treatment has what probability of being the best;

• maintain randomization;

• avoid financial investment in randomized studies (allows indirect comparisons in the absence of face-to-face clinical trials);

• time saving of analysis vs clinical trial;

• in the case of equality between the results of the two methods, it is possible to construct a global estimator which combines the results of the approaches taking into account all of the available information.

2.3. Direct and indirect comparison

In multiprocessing meta-analyzes, there are two main comparison approaches: the direct approach and the indirect approach.

Definition 1. (Direct comparison).

The direct approach is performed when the two treatments A and B are compared directly in an RCT (randomized clinical trial) to compare the effectiveness of the two treatments, and among the properties of the meta-analyzes in direct comparison:

• optimization of tests already carried out;

• saving of resources and time;

• gain in power;

• reuse of results for economic modeling purposes;

•tool to aid decision.

Definition 2. (The indirect comparison).

In the indirect comparison approach, the efficacy of the two treatments A and B is compared through the respective efficacy of the two treatments against a common control, most often a placebo, and among the properties of the meta - indirect comparison analyzes it is found that the randomization is partially maintained.

Definition 3. (The inconsistency).

The inconsistency of the network reflects the discrepancy between the results of direct comparisons and indirect comparisons concerning a pair of treatments.

The absence of the inconsistency (inconsistency) detected strengthens the confidence that one can have in the results (simplified the mixed comparison). To detect the presence of inconsistency, there are several methods such as the method of (Song, F., A. J. Eastwood, et al,

2000), that of (Glenny, 2005) and the method of Bucher which uses direct and indirect approaches simultaneously to detect the inconsistency.

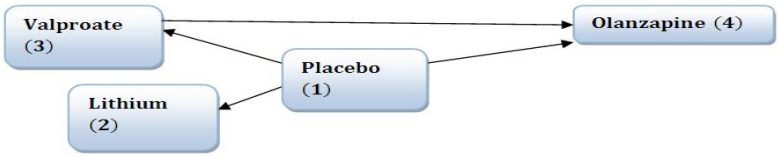
3. Effectiveness through a treatment network

3.1. The multiprocessing comparison (MTC)

According to the network meta-analysis methodology, the multi-treatment combination method is used when all patients in the clinical trials are target populations for analysis.

We are building the following network:

Figure 2. The mixed treatment comparison « MTC ».



Source: Produced by the authors.

In this study, we used 23 clinical trials (see Table 1 in the appendix) for the mixed comparison between four pharmaceuticals, the placebo and three antiepileptic treatments (valproate, lithium, olanzapine). The network meta-analysis data applied in this thesis can be found in the reference: (Soares-Weiser and al, 2007). We pose:

δ : the observed effect of treatment.

Θ : The true effect of the treatment.

ξ^2 : the inter-assay variance.

τ^2: the intra (between) -assay variance.

n_{ik}: the number of individuals in the trial i and the arm k.

r_{ik} : the number of events in the trial i and the arm k.

p_{ik}: the probability of an event in the trial i and the arm k.

μ_i : the mean of the event rate of trial i in the logit scale.

Sous l'hypothèse de la vraisemblance binomiale suivante :

$$r_{ik} \sim binomial(p_{ik}; n_{ik})$$

The random effects model is written in the form:

$$logit\ (p_{ik}) = \mu_i + \delta_{i,1k} \mathbb{1}_{\{k \neq 1\}};\ \delta_{i,1k} \sim \mathcal{N}\left(\Theta_{t_{i1} t_{ik}}; \tau^2\right) \qquad (6)$$

where

$$\mathbb{1}_{\{s\}} = \begin{cases} 1 & \text{if } s \text{ is right} \\ 0 & \text{if not} \end{cases}$$

The fixed effects model is written in the form:

$$logit\ (p_{ik}) = \mu_i + \Theta_{t_{i1} t_{ik}} \mathbb{1}_{\{k \neq 1\}} \qquad (7)$$

In the multiple case we use the equation $\Theta_{t_{i1}t_{ik}} = (\Theta_{t_{ik}} - \Theta_{t_{i1}})$, because we are trying to calculate two-by-two comparisons between interventions.

The random effects model is written in the general form:

$$\begin{cases} \alpha_{ik} = \mu_i + \delta_{i,1k}\mathbb{1}_{\{k\neq 1\}} \\ \delta_{i,1k} \sim \mathcal{N}\left(\Theta_{t_{ik}} - \Theta_{t_{i1}}; \tau^2\right); i = 1, \dots, 23 \\ \Theta_{t_{ik}} \sim \mathcal{N}(0; 10^{-4}), \Theta_{t_{i1}} \sim \mathcal{N}(0; 10^{-4}), k = 1,2 \\ \tau \sim u\ niforme(0; 5), \mu_i \sim \mathcal{N}(0; 0{,}001) \end{cases}$$

$\alpha_{ik} = logit\ (p_{ik})$ is the linear predictor.

Table 1. Estimation of the parameters of the random effects model[4].

Paramètres	median	INC[5] $[2,5\%; 9\ 75\%]$
OR[1,2]	0,071	$[0{,}002; 2{,}106]$
OR[1,3]	0,32	$[0{,}011; 7{,}212]$
OR[1,4]	0,395	$[0{,}014; 9{,}951]$
OR[2,3]	4,459	$[0{,}112; 150{,}1]$
OR[2,4]	5,496	$[0{,}144; 210{,}5]$
OR[3,4]	1,233	$[0{,}053; 33{,}96]$
τ	1,367	$[0{,}002; 2{,}106]$

Interpretation of odds ratio (OR) parameters:

The odds ratio[6] of Lithium to Placébo is equal to 0.0718, on the other hand the odds of placebo is 13.91 = (1/0.071 8) times less.

The odds ratio of Valproate to Placébo is 0.32, on the other hand, the odds of placebo is 3.12 times less.

The odds ratio of Olanzapine to Placébo is 0.395, on the other hand, the odds of placebo is 2.528 times less.

The odds ratio of Valproate to Lithium is 4.46.

The odds ratio of Olanzapine to Lithium is 5.49.

The odds ratio of Olanzapine to Valproate is 1.233.

The intra (between) -assay variance is equal to τ ^ 2 = 2.06> 0, so there is heterogeneity between trials.

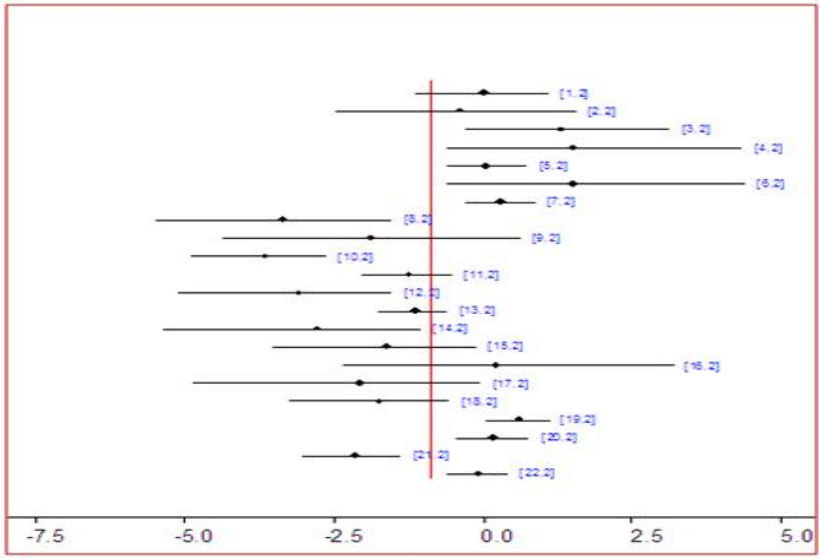
[4]The results in the table are obtained after 50,000 iterations (Gibbs sampling is used).

[5] INC: Credibility interval

[6] The odds ratio is a measure of relative effect, an odds ratio of 1 corresponds to no effect. In the event of a beneficial effect, the odds ratio is less than 1 and it is greater than 1 in the event of a deleterious effect. The further the odds ratio is from 1, the greater the effect.

The following graph provides the treatment effect for each trial in the random-effects model, such that trials 1 to 7 compare Olanzapine versus Valproate, the remaining trials successively compare lithium (8 to 12), Olanzapine (from 13 to 18) and Valproate (from 19 to 22) compared to the placebo.

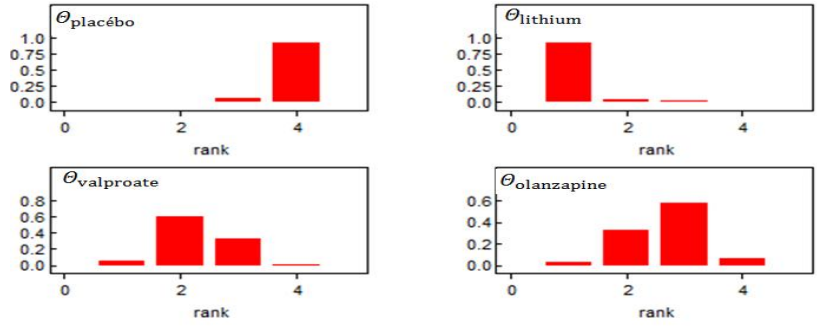
Figure 3. Estimation of the parameters of the random effects model[7].



This figure can be used to calculate the relative weight (with random effects) of the different tests and therefore to calculate the benchmark test.

3.2. The Bayesian classification of treatments

Figure 4. Classification histograms (in English, rankogram) for: placebo, lithium, valproate, olanzapine, successively.



To analyze the results of FIG. 5, the area under the curve of the cumulative rank probabilities is used for each treatment "surface under the cumulative ranking: SUCRA".

[7] The results in the table are obtained after 50,000 iterations (Gibbs sampling is used).

The following table shows the four classification histograms with digits according to the treatments and the ranks.

Table 2. The classification probabilities for each drug.

% Probabilité	Placébo	Lithium	Valproate	Olanzapine
j=1	0	0,9	0,06	0,04
j=2	0	0,07	0,6	0,33
j=3	0,083	0,03	0,32	0,567
j=4	0,917	0	0,02	0,063

For each treatment and each rank, the sum of the probabilities is equal to 1. The cumulative table is used to determine the distribution function associated with each treatment.

Table 3. The repartition function for each drug.

% Probabilité	Placébo	Lithium	Valproate	Olanzapine
j=1	0	0,9	0,06	0,04
j=2	0	0,97	0,66	0,37
j=3	0,083	1	0,98	0,937
j=4	1	1	1	1

We calculate each time the integral under the repartition function adjusted for each treatment from the previous table, we find:

$$F_{\textbf{Placebo}}(x) = 0{,}229x^2 - 0{,}838x + 0{,}6463\,; R^2 = 0{,}96$$

$$S(2) = \int_2^4 \left(0{,}229x^2 - 0{,}838x + 0{,}6463\right)dx = 0{,}0835.$$

$$F_{\textbf{Lithium}}(x) = -0{,}0175x^2 + 0{,}12x + 0{,}797;\ R^2 = 0{,}99$$

$$S(4) = \int_1^4 (-0{,}0175x^2 + 0{,}12x + 0{,}797)dx = 2{,}88.$$

$$F_{\textbf{valproate}}(x) = -0{,}145x^2 + 1{,}039x - 0{,}835;\ R^2 = 1$$

$$S(4) = \int_{1}^{4} (-0{,}145x^2 + 1{,}039x - 0{,}835)dx = 1{,}848.$$

$$F_{\textbf{olanzapine}}(x) = 0{,}7447\ ln(x) - 0{,}0049\ ;R^2 = 0{,}94$$

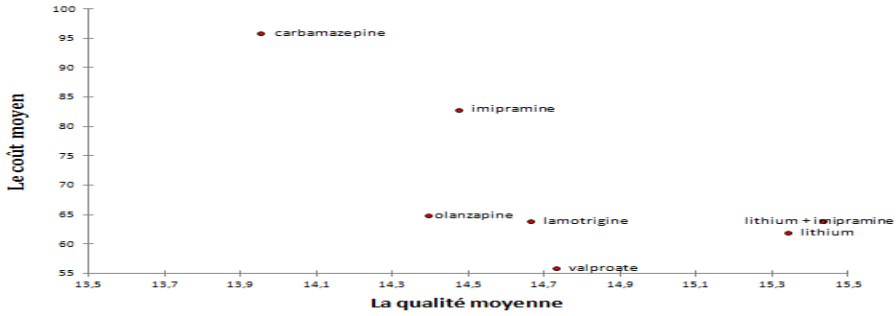
$$S(4) = \int_{1}^{4} \left(0{,}7447\ ln(x) - 0{,}0049\ \right)dx = 1{,}468.$$

Table 5. Classification of drugs according to the SUCRA criterion.

Traitement	SUCRA[8](%)
Placebo	**4%**
Lithium	**96%**
Valproate	**61,6%**
Olanzapine	**48,9%**

SUCRA (Surface Under the Cumulative Ranking): is a parameter used to rank the treatments according to their probability of ranking first, second,... etc. The SUCRA ranges from 0% (i.e. treatment always ranks last) to 100% (i.e. treatment always ranks first). According to the table Lithium is superior to other drugs in terms of effectiveness and Valproate is likely to be superior to Olanzapine for the disease concerned, finally the placebo has a low probability which means that the placebo always ranks last. The following figure shows the relationship between the average cost (£), and the average quality (by survival analysis) of some antiepileptic drugs.

Figure 5. The relationship between the average cost and the average quality of some antiepileptic drugs.



Source: (Soares-Weiser and al, 2007).

[8]SUCRA is calculated from the MenuMath program where S (n) = approximation of the integral a to b of f (x) dx by n intervals.

Discussion

Each treatment at a cost to the country budget and cost rationalization is an important objective, especially the very expensive prices of pharmaceuticals for epilepsy diseases in the international market. From the results, lithium is the most important drug because of efficacy (the best treatment by SUCRA criteria) and cost. Lithium salt has been used for 50 years for the prevention against the bipolar discordant relapse "relapse of bipolardisorder", the British association of psychopharmacology (BAP) is posed in their guide lithium in the first line for the fight against the discorder bipolar. This study confirms the findings of the British Psychopharmacology Association on the efficacy of lithium and shows the importance of this type of statistical analysis. On the other hand, the importance of the method used and in the article itself is the Bayesian approach such that in this approach to measurement, an observation transforms this information a priori into a posteriori. This concept does not differentiate between parameters and observations in kind: they are random variables. The estimation problem is then solved in a simple way. The Bayesian approach in clinical trials is of great interest in the development of medical production, as it offers valid information and allows reducing the number of necessary subjects particularly interesting by small target populations. The performance of this approach, which combines existing information and data provided by the current trial, is recognized in all phases of clinical trials and more particularly in the last phase (pharmacovigilance), where the Bayesian approach makes it possible to calculate quantitatively the strength of an association between an adverse effect and a drug within the database, thus detecting an adverse effect more quickly, while reducing the risk of false positives.

Results

This work with the meta-analysis has allowed us to understand why health technology assessment agencies and regulatory bodies are also confronted with these synthesis methods. In the results of this work, we find:

1. The multi-treatment meta-analysis approach seems relevant for:

- analyze the efficacy from data from different trials on identical treatments;
- look for an interaction between the effect of the treatment and covariates defined at the trial or patient level;
- classify the treatments according to the best probabilities (the SUCRA method);
- Estimate the efficiency for comparisons that have rarely or never been carried out in practice.

2. The multi-treatment comparison confirms the results of the British Psychopharmacology Association on the efficacy of lithium.

References:

Adams M.E, McCall N.T, Gray D.T et al. (1992). Economic analysis in randomized controlled trials. Medical Care, 30:231-243.

Begin, J .F. (2010). Analyse MCMC de certains modèles de diffusion avec application au marché Européenne du carbone. Canada: Rapport Technique, Université de Montréal.

Buxton M.J, Drummond M.F, van Hout B.A, Prince R.L, Sheldon T.A, Szucs T, Vray M. (1997). Modelling in economic evaluation: an unavoidable fact of life. Health Economics, 6: 217-227.

Drummond, M. F., & Davies, L. . (1991). Economic analysis alongside clinical trials: revisiting the methodological issues. . International journal of technology assessment in health care, 7(4), 561-573.

Glenny, A. M. (2005). Indirect comparisons of competing interventions . Health Technol, 9 (26): 1 –iv.

Higgins, J. P. and A. Whitehead. (1996). Borrowing strength from external trials in a meta-analysis. Stat Med, 15(24): 2733-2749.

Lu, G. and A. E. Ades. (2004). Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med, 23(20): 3105-3124.

Quilici, S. (2012). Avancées récentes ،les méta-analyses multitraitements. Tirer parti de toute l'information en économie de la sante : introduction aux outils statistiques Bayésiens. Paris: Séminaire JEM SFES.

Sheldon T.A. (1996). Problems of using modelling in the economic evaluation of health care. Health Economics;, 5: 1-11.

Soares-Weiser and al. (2007). A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder. Health Technology Assessment, 11(39).

Song, F., A. J. Eastwood, et al. (2000). Publication and related biases. Health Technol Assess , 4 (10): 1 -115.

Whitehead, A. (2002). 'Meta-analysis of Controlled Clinical Trials. Chichester, UK: John Wiley & Sons, Ltd, World Health Organization International Clinical Trials Registry Platform.

Appendices

Table 1. Multi-treatment meta-analysis data.

Trials	Traitements		Control group		Treatment group	
	Traitements (1,3)	Traitements (2,3,4)	death	total	death	total
1	Valproate	Olanzapine	13	20	20	31
2	Valproate	Olanzapine	2	1	10	10
3	Valproate	Olanzapine	2	6	10	10
4	Valproate	Olanzapine	0	3	10	13
5	Valproate	Olanzapine	106	106	126	125
6	Valproate	Olanzapine	0	3	10	13
7	Valproate	Olanzapine	25	31	126	125
8	placebo	Lithium	17	3	18	9
9	placebo	Lithium	7	1	11	2
10	placebo	Lithium	101	31	104	70
11	placebo	Lithium	44	18	69	49
12	placebo	Lithium	120	56	119	66
13	placebo	Olanzapine	72	18	225	136
14	placebo	Olanzapine	17	0	225	136
15	placebo	Olanzapine	9	1	225	136
16	placebo	Olanzapine	0	1	225	136
17	placebo	Olanzapine	5	0	225	136
18	placebo	Olanzapine	18	2	225	136
19	placebo	Valproate	45	36	187	94
20	placebo	Valproate	33	21	187	97
21	placebo	Valproate	71	6	187	94
22	placebo	Valproate	71	35	187	94
23	placebo	Valproate	13	6	120	10

Source: (Soares-Weiser and al, 2007)

Bipolar disorder, formerly called manic depression, is a mental health condition that causes extreme mood swings that include emotional highs (mania or hypomania) and lows (depression).

The code on the OpenBUGS program

```
model{
for(i in 1:ns){
w[i,1] <- 0
delta[i,1] <- 0
mu[i] ~ dnorm(0,.0001)
for (k in 1:na[i]) {
r[i,k] ~ dbin(p[i,k],n[i,k])
logit(p[i,k]) <- mu[i] + delta[i,k]
rhat[i,k] <- p[i,k] * n[i,k]
```

```
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
}
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]) {
delta[i,k] ~ dnorm(md[i,k],taud[i,k])
md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
taud[i,k] <- tau *2*(k-1)/k
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
sw[i,k] <- sum(w[i,1:k-1])/(k-1)
}
}
totresdev <- sum(resdev[])
d[1]<-0
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)
tau <- pow(sd,-2)
delta.new[1] <- 0
w.new[1] <- 0
for (k in 2:nt) {
delta.new[k] ~ dnorm(m.new[k],tau.new[k])
m.new[k] <-  d[k] + sw.new[k]
tau.new[k] <- tau *2*(k-1)/k
w.new[k] <- delta.new[k] - d[k]
sw.new[k] <- sum(w.new[1:k-1])/(k-1)
}
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
lor.new[c,k] <- delta.new[k]- delta.new[c]
or.new[c,k] <- exp(lor.new[c,k])
}
}
p.base ~ dbeta(a,b)
a <- r[ns+1,1]
```

```
b <- n[ns+1,1]-r[ns+1,1]
for (k in 2:na[ns+1]) {
logit(p.new[k]) <- logit(p.base) + (delta.new[t[ns+1,k]]- delta.new[t[ns+1,1]])
r.new[k] ~ dbin(p.new[k], n[ns+1,k])
# value observed (r[ns+1,2]),
p.cross[k] <- step(r[ns+1,2] - r.new[k]) - 0.5*equals(r.new[k],r[ns+1,2])
}
}
```