Université de Montréal

Examen de l'effet de potentialisation des médicaments antipsychotiques par les inhibiteurs de la recapture de la sérotonine pour traiter les symptômes négatifs de la schizophrénie : approche méta-analytique.

Par

Amir Ali Sepehry

Département de sciences biomédicales: Option sciences psychiatriques

Faculté de médicine

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Examen de l'effet de potentialisation des médicaments antipsychotiques par les inhibiteurs de la recapture de la sérotonine pour traiter les symptômes négatifs de la schizophrénie : approche méta-analytique.

Présentée par :

Amir Ali Sepehry

A été évaluée par un jury composé des personnes suivantes :

François Lespérance, MD., président-rapporteur
Dr. Emmanuel Stip, MD, MSc, CSPQ., directeur de recherche
Lahcen Aït Bentaleb, MD, PhD., membre du jury

Résumé

Parmi les signes qui font partie de la définition clinique de la schizophrénie, figurent les symptômes négatifs. Ces symptômes négatifs (le retrait social, l'émoussement des affects, l'avolition, etc.) sont des signes qui sont difficiles à traiter. Différentes stratégies médicamenteuses ont été proposées. Dans ce mémoire de maîtrise, nous avons examiné une des modalités de potentialisation de l'effet habituel des médicaments antipsychotiques sur les symptômes de la schizophrénie pour traiter ces symptômes négatifs. Les médicaments que nous avons étudiés en tant que potentialisateurs sont les inhibiteurs sélectifs de la recapture de la sérotonine (ISRS) qui sont habituellement prescrits pour traiter les épisodes dépressifs majeurs mais qui ont également été essayé dans le traitement des symptômes négatifs de la schizophrénie. Les résultats d'essais contrôlés de cette potentialisation ont fait l'objet de plusieurs publications et nous avons voulu, dans le cadre de cette maîtrise, faire l'examen de l'effet de la potentialisation des médicaments antipsychotiques par les ISRS pour traiter les symptômes négatifs en utilisant une approche de revue de littérature quantitative que l'on désigne de méta analyse. Dans ce mémoire, nous avons rédigé une mise à jour de la méthodologie propre aux méta-analyses conformément aux critères établis par le groupe Cochrane. Nous avons pu ainsi définir quelles étaient les étapes nécessaires à diriger une méta-analyse avec un ensemble de données continues. Nous avons détaillé l'ensemble de ces étapes et appliqué par la suite l'approche méta analytique à l'hypothèse suivante: est-ce que les ISRS, lorsqu'ils sont utilisés pour potentialiser les médicaments antipsychotiques pour traiter les symptômes négatifs dans la schizophrénie sont efficaces.

En recueillant les études de la façon la plus exhaustive possible et en réunissant le nombre de patients impliqués dans ses études, sélectionnés en fonction de critères d'exclusion et d'inclusion, nous avons abouti aux résultats suivants:

Onze études ont répondu à nos critères d'inclusion. Avec le modèle d'effet aléatoire, le taille de l'effet obtenue mesurant les changements de l'intensité des symptômes négatifs était non-significative (N= 393; Hedges' g= 0.178; p= 0.191). Cependant, quand des études ont été divisées selon la sévérité de la maladie, une taille de l'effet modérée a émergé significativement pour les études faisant participer des patients désigné 'chroniques' (N= 274; Hedges' g= 0.386; p= 0.014).

En conclusion, la méta-analyse que nous avons réalisée et publiée montre un effet négligeable de l'addition des ISRS au traitement antipsychotique habituel pour traiter les symptômes négatifs de la schizophrénie. Dans la discussion nous analysons les limites et les conséquences de ces résultats.

Mots-clés : Schizophrénie, poly-thérapie, méta-analyses, antipsychotique, inhibiteurs sélectifs de la recapture de la sérotonine, ISRS.

Résumé (English)

The negative symptoms of schizophrenia (social withdrawal, flat affect, avolition, etc.) are difficult to treat. Various medication strategies have been proposed. In this manuscript, we examine one of the methods of potentiation of antipsychotic drugs for the treatment of the negative symptoms in schizophrenia. The drugs which were studied as potentiation agents are the monoamine selective serotonin reuptake inhibitors (SSRIs) which are primarily prescribed to treat major depressive episodes, but are also prescribed in the treatment of the negative symptoms of schizophrenia. Several controlled clinical trials examining the effects of SSRIs in schizophrenia were published. This manuscript, examines the effect of potentiation of the antipsychotic agents, via SSRIs for the treatment of negative symptoms using a quantitative systematic review of the literature.

The meta-analytic method used is in accordance with the criteria established by Cochrane. Additionally, stages necessary to direct meta-analysis with continuous data were brought into prominence. Consequently, we have applied the meta-analytic approach to the following assumption: SSRIs are effective when they are used as a potentiation agent to antipsychotic drugs to treat the negative symptoms in schizophrenia.

Subsequently, by investigating exhaustively the available studies and using inclusion (a- SSRI add-on therapy was compared with antipsychotic monotherapy among schizophrenia spectrum disorder patients; b- the clinical trials were randomized, double blind, placebo-controlled with parallel-arm design; c- negative symptoms were assessed with the Sacle for the Assessment of the Negative Symptom or Positive and Negative

Syndrome Scale-negative subscale) and exclusion criteria (1- schizophrenia with comorbidity; 2- incomplete or unavailable data; 3- comparison with other compounds such as MAOI; 4- cross-over studies), we could, by aggregating the number of patients involved in the selected studies, realize a meta-analysis:

Eleven (n=11) studies reached inclusion criteria. Within a random-effect model, a non-significant composite effect size estimate (end-point) for negative symptoms was obtained (N= 393; adjusted Hedges's g= 0.178; p= 0.191). However, when studies were divided according to severity of illness, a moderate and significant composite effect size emerged for the studies involving the so-called "chronic patients" (N= 274; adjusted Hedges's g= 0.386; p= 0.014).

In conclusion, with the attached published meta-analysis, we have demonstrated an insignificant effect for add-on therapy with SSRI's with antipsychotic medication for treatment of negative symptoms in schizophrenia. Hence, in the discussion, we have analyzed the limitation and consequences of our results.

Keywords: Schizophrenia, Polytherapy, Meta-analysis, Antipsychotic, Selective serotonin reuptake inhibitors, SSRI.

Liste des abréviations

ANOVA (F) : Analysis of Variance

BDI : Beck Depression Inventory

BPRS : Brief Psychiatric Rating Scale

CGI : Clinical Global Impression

CI : Confidence Interval

CMA : Comprehensive Meta-Analysis

CNS : Central Nervous System

d : Cohens'*d*

D : Dopamine

DF (df) : Degrees of Freedom

DSM : Diagnostic and Statistical Manual

EMBASE : Excerpta Medica dataBase

EPS : ExtraPyramidal Symptoms,

ES : Effect Size

FDA : Food and Drug Administration

g : Hedges' *g*

HAM-D: Hamilton Rating Scale for Depression

In : Inpatients

ISRS : Inhibiteurs Sélectifs de la Recapture de la Sérotonine

ITT : Intention To Treat

LOCF : Last Observation Carried Forward

M : Mean

MADRS : Montgomery-Åsberg Depression Rating Scale

MAOI : MonoAmino Oxidase Inhibitors

mPFC : medial Prefrontal Cortex

MATRICS : Measurement and Treatment Research to Improve Cognition in schizophrenia

N (n) : sample size

NIMH : National Institute of Mental Health

NNT : Number Needed to Treat

OCD : Obsessive Compulsive Disorder

OR : Odd-Ratio

P : Probability

PANSS : Positive And Negative Symptoms Scale

PLC : Placebo group

PT : Patients

QUOROM : QUality Of Reporting Of Meta-analyses

RCT : Randomized Controlled Trials

RD : Risk Difference, also called absolute risk reduction

RR : Relative Risk

S-A : Simpson-Angus extrapyramidal effects

SANS : Scale for the Assessment of Negative Symptoms

SAPS : Scale for the Assessment of Positive Symptoms

SD : Standard Deviation

SMD : Standardized Mean Difference

SOHO : Schizophrenia Outpatient Health Outcomes

SSRI : Selective Serotonin Reuptake Inhibitor

TCA : Tricyclics

TX : Treatment

UKU : Udvalg for Kliniske Undersogelser

σ : sigma

δ : delta

5-HT : Serotonin

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La dédicace

I would like to dedicate this manuscript to people who suffered in their life from such a debilitating illness.

Remerciements

Throughout the groundwork of the manuscript, I was privileged to have the guidance of several colleagues and friends who read the material and offered sound suggestions. Nonetheless, I would like to divide my attention in this matter into 3 foci, academic, personal, and professional.

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Introduction

In order to increase the efficacy of antipsychotic medication in treatment of schizophrenia in both clinical and research settings, polytherapy [more precisely poly-pharmacy or add-on therapy] is a common avenue for treatment. A recent German study by Messer and colleagues underlined the fact that 40 - 50 % of schizophrenia inpatients and close to 90 % of schizophrenia outpatients were treated with antipsychotic combination therapies (Messer, Tiltscher and Schmauss 2006). Our interest lays in add-on polypharmacy with selective serotonin reuptake inhibitors (SSRI), for controlling negative symptoms. Literature argues that this approach in treatment is limited and thus making evidence-based treatment decision difficult (Buckley and Stahl 2007). In general, very few well designed published studies address the limitations of SSRI polypharmacy in schizophrenia. To that end, most studies are case reports, clinical trials with poor methodology (e.g., pilot studies, cross-over designs, or open trials), often with small sample sizes that are not generalizable. The inconclusiveness of the results makes evidence-based decision making difficult. Thus, conducting a meta-analysis is warranted.

Using a meta-analytical approach, by converting results of randomized controlled trials (RCT) to common metrics (effect size: ES) that would facilitate 'generalizability'; hence provide information for future studies. As Peto (Peto 1987) explains, generation of a global output based on moderating variables would help in improving clinical decision making.

Using meta-analysis to investigate moderating variables, we aim to assess the quality of research methods and clinical approaches in those studies, and possibly ascertaining other factors leading to result discrepancies.

In this vein, a synopsis of the literature on SSRI add-on therapy used for control of negative symptoms will be presented with reference to our article. To begin, the reasons for using SSRI add-on therapy will be discussed. Next, assessment strategies (scales) of the negative symptoms of schizophrenia will be explained. Finally, we will elaborate on the rational behind using meta-analysis to answer the above mentioned clinical-research queries. In addition, we will briefly review meta-analytic techniques (Bent, Shojania and Saint 2004) and answering a series of intricate questions (Maier 2006), related to antipsychotic add-on therapy.

Symptômes négatifs de la schizophrénie

Since Bleuler, negative symptoms (apathy, reduced volition and motivation, anergia, alogia, blunted affect and social withdrawal) in schizophrenia have been considered to be the core features of the disease (Bleuler 1950). According to Kirkpatrick and colleagues (Kirkpatrick, Fenton, Carpenter and Marder 2006), primary negative symptoms represent about 20-25% of patients suffering from schizophrenia. Particularly difficult to treat, these symptoms represent significant obstacles in achieving better global functioning (Bottlender, Wegner, Wittmann, Strauss and Moller 1999; Moller, Bottlender, Gross, Hoff, Wittmann, Wegner and Strauss 2002), quality of life, social and occupational functioning (Buchanan and Gold 1996).

Several studies demonstrated a correlation between negative symptoms and neurocognitive performance in schizophrenia (Liddle 1987; Liddle, Barnes, Speller and Kibel 1993; Cuesta and Peralta 1995; Baxter and Liddle 1998). Neuropsychological performance in several domains (e.g., memory, executive function, attention) has been reported to be a cardinal deficiency in schizophrenia (Green 1998), associated with poor functional outcome (Green 1996; Green, Kern, Braff and Mintz 2000), and work performance (McGurk and Meltzer 2000). For example, Stip reports a positive correlation between temporal organizations (executive task) and negative symptoms (Stip 2006), whilst Stirling and colleagues, report on significant association of memory impairment to negative symptoms (Stirling, Hellewell and Hewitt 1997). This neurocognitive association with negative symptoms complicates treatment. Moreover, negative symptoms seem to emerge

from a distinctive pathophysiological pattern associated with etiological risk factors (e.g., genetics) (Kendler, Gruenberg and Tsuang 1986).

First-generation antipsychotic drugs [also called typical or conventional neuroleptics] provide only minimal relief of negative symptoms (Meltzer, Sommers and Luchins 1986). Second-generation antipsychotic drugs [sometimes called atypical] have been developed in an attempt to decrease side-effects of typical neuroleptics, and to improve negative symptoms and cognitive performance. That having been said, negative symptoms remain mostly refractory to treatment (Moller 2004). This can be explained by the heterogeneity of subcategories of negative symptoms in response to treatment regimens. Meta-analytical studies have reported the potential benefits of second-generation antipsychotics in the treatment of negative symptoms. Nevertheless, these benefits appeared to be modest (Leucht, Pitschel-Walz, Abraham and Kissling 1999; Geddes, Freemantle, Harrison and Bebbington 2000).

The role of antidepressant drugs as an adjunctive treatment of negative symptoms has been discussed by Siris and later by Silver (Siris, van Kammen and Docherty 1978; Silver 2003). In clinical practice, it has been estimated that antidepressants are prescribed as adjunctive treatment in approximately one-third of patients (Addington, Azorin, Falloon, Gerlach, Hirsch and Siris 2002). However, add-on therapy with antidepressants such as monoamine oxidase inhibitors (MAOI) (Brenner and Shopsin 1980) or tricyclics (TCA) (Evins 1996) in schizophrenia have shown to have limited efficacy (Siris, Bermanzohn,

Gonzalez, Mason, White and Shuwall 1991). More recently, SSRIs have been investigated as "augmentation therapy" for the negative symptoms in schizophrenia.

Hence, we have conducted a meta-analysis by aggregating data from the existing literature, in order to determine the effect of SSRI add-on therapy for the negative symptoms.

Évaluation des symptômes négatifs

There are several scales available for research and clinical purposes in order to identify and measure changes in the negative symptoms of schizophrenia (Andreasen and Olsen 1982) or deficit form schizophrenia (Carpenter, Heinrichs and Wagman 1988) or type II schizophrenia (Crow 1985). Some of these scales help in diagnosis of patients with "deficit syndromes", or rate the severity of the negative symptoms. Others such as scale for the assessment of negative symptoms (SANS) were developed to facilitate the measurement of changes in negative symptoms. These scales can be categorized as self-rating scales such as subjective experience deficits in schizophrenia scale developed by Liddle and Barnes (Liddle and Barnes 1988); and include subjective deficit syndrome scale whereas others are observer-based rating scale (e.g., SANS).

Each negative symptom scale usually reflects a particular theoretical approach to negative symptoms. For our meta-analysis, we have selected the SANS, first developed in 1982 by Nancy Andreasen (Andreasen 1982). The original version of SANS provides both subjective (Andreasen 1982) (5 items) and raters evaluation of negative symptoms (25 items). Although, to date, there are no clear guidelines for the evaluation of negative symptoms using SANS, it remains the most frequently used scale for the assessment of negative symptoms in pharmacological research. Several negative symptom constructs are ascertained, with multiple items related to each. The inclusion of more than 1 item improves the psychometrics properties of the scale. It is noteworthy that the SANS has more items (30 items, original version) than most other rating scales (such as BPRS with 3 items, or PANSS with 7 times), and moderate to high inter-rater reliability in patient

assessment (Lecrubier and Boyer 1987; Lecrubier 1997; Silk and Tandon 1991) as well as short-term pharmaceutical trials (Lindenmayer 2001).

Polypharmacie avec les ISRS

Perspective clinique

It is clear that the treatment/control of negative symptoms of schizophrenia remains a substantial challenge for the clinician (Lublin, Eberhard and Levander 2005) (Erhart, Marder and Carpenter 2006). In this context, a variety of treatment approaches as monotherapy with pharmacological agents, as traditional antipsychotics and later followed by atypical antipsychotics have been carried out. Traditional antipsychotics such as haloperidol (high-potency) and chlorpromazine (low-potency) are initially prescribed in order to control the psychotic, positive (those added to the normal personality) and negative symptoms (those that deduct from normal personality) of schizophrenia, yet they have undesired side-effects (e.g., extrapyramidal symptoms, EPS), and some patients continue to have persisting schizophrenia symptoms. Additionally, their strong dopamine D2 receptor blockade causes or induces negative symptoms similar to the deficit symptoms of schizophrenia (Schooler 1994). Knowing this, novel antipsychotics, characterized by selective action on neurotransmitters were introduced (e.g., serotoninergic, dopaminergic). This was based on lower dopamine D2 receptors occupancy and a better potency as serotonin (5-HT) type 2a antagonists, in combination to improve efficacy and tolerability for the control of schizophrenia symptoms (Haro, Edgell, Novick, et al, 2005). Yet, in select patients, negative symptoms, persist or remain stable over time during treatment (Arndt, Andreasen, Flaum, Miller and Nopoulos 1995; Silver 2003). Although patients treated with atypical antipsychotics were more responsive than patients treated with traditional neuroleptics, some patients manifested persisting negative symptoms. However,

Moller and colleague' retrospective study using path analysis provided evidence of a direct effect of second generation antipsychotics on persisting negative symptoms (Moller, Muller, Borison, and Chouinard, 1995). Yet, they came with limitations, for instance, these studies were carried-out with patients suffering from both positive and negative symptoms (Lecrubier, Quintin, Bouhassira, Perrin, and Lancrenon 2006). Consequently, clinical researchers argued as to whether negative symptoms were due to the same underlying pathophysiology as positive symptoms, or simply a side effect of pharmacological agents (Carpenter, Heinrichs and Wagman 1988; Barnes and McPhillips 1995). Kirkpatrick et al and others proposed specific criteria for diagnosing negative symptoms (Carpenter, Heinrichs et al. 1988; Kirkpatrick, Buchanan, McKenney, Alphs and Carpenter 1989). They noted that at least 2 of the 6 primary enduring negative symptoms [restricted affect, diminished emotional range, poverty of speech, curbing of interests, diminished sense of purpose, and diminished social drive] must be present or the persistence of a combination of two or more symptoms in the past 12 months. Furthermore, the patients have to meet the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for schizophrenia. And lastly, these symptoms are not secondary to co-morbid disorders such as anxiety, EPS, positive symptoms, mental retardation, and depression. Thus, these concise criteria separated primary from secondary negative symptoms. Supporting the necessity of such separation was Siris, who suggested that clinical trials should implement appropriate measures to control for confounding variables such as depression (Siris 1991). Since the neurobiological basis of negative symptoms remain unclear (Tandon and Greden 1989),

phase III clinical trials comparing atypical to typical antipsychotic agents were initiated. Few attempts at comparing traditional antipsychotics to atypical antipsychotic (selective D2 blockers) such as Remoxipride were made (Lecrubier, Quintin, Bouhassira, Perrin, Lancrenon 2006). Although the effect of Remoxipride was similar to haloperidol on positive symptom and persisting negative symptoms, it showed fewer side-effects (Ahlfors, Rimon, Appelberg, Hagert, Harma, Katila, Mahlanen, Mehtonen, Naukkarinen, Outakoski and et al. 1990; Lewander, Westerbergh and Morrison 1990; Kane 1993). Nonetheless other authors reported contradictory results (Chouinard 1990). For example, Lapierre and colleagues showed that clinical trials supporting the idea that Remoxipride is beneficial in treating persisting negative symptoms was not sufficient to establish its efficacy (Lapierre, Ancill, Awad, Bakish, Beaudry, Bloom, Chandrasena, Das, Durand, Elliott and et al. 1992). Other studies showed positive results of the atypical, when targeting primary negative symptoms (Lapierre, Angus, Awad, Saxena, Jones, Williamson, Vincent, Carle, Lavallee, Manchanda, Gauthier, Wolf, Teehan, Denis, Malla, Oyewumi, Busse, Labelle, Claesson and Grafford 1999). The later studies had several limitations, for example, they were conducted with small sample size that could not provide robust conclusions as to whether or not these agents are efficient for treatment of persisting negative symptoms. To date antipsychotics alone have not credibly resolved the problem of persisting negative symptoms (Leucht, Pitschel-Walz et al. 1999; Carpenter 2004), consequently encouraging the use of alternative therapeutic methods. That having being said, the Food and Drug Administration (FDA) endorsement for an indication of negative symptoms and available

data, indicate that second generation antipsychotics have not yet met early hopes for a highly effective management compound for easing of negative symptoms (Laughren and Levin 2006). Moller found that non-responsive patients constituted a subgroup that was often responsive to dual treatment (Moller 2004).

Polypharmacy with SSRI for treatment of negative symptoms in schizophrenia was introduced. The clinical underlying principle for the use of antidepressant add-on therapy is based on the primary / secondary dichotomy. Negative symptoms are classified as primary or secondary (Carpenter, Heinrichs et al. 1988; Kirkpatrick, Buchanan et al. 1989). In contrast with primary negative symptoms, which are directly related to the schizophrenia pathophysiology, secondary negative symptoms result from other psychiatric symptoms (e.g. positive symptoms), medication side-effects (e.g. extrapyramidal symptoms) or medical conditions (e.g. mental retardation) (Carpenter, Heinrichs et al. 1988; Kirkpatrick, Buchanan et al. 1989). In particular, negative symptoms may be secondary to depressive symptoms, which share common key symptoms such as anhedonia-asociality and avoilition-apathy (Kitamura and Suga 1991; Sax, Strakowski, Keck, Upadhyaya, West and McElroy 1996). In this context, the use of antidepressants has been thought to be of potential interest in schizophrenia, as the treatment of depressive symptoms would eventually lead to a relief of secondary negative symptoms.

Based on preliminary results, Silver has proposed the usage of SSRI augmentation therapy for these enduring symptoms (Silver 2003). However, other studies published so far have produced conflicting results (Spina, De Domenico, Ruello, Longobardo, Gitto,

Ancione, Di Rosa and Caputi 1994; Lee, Kim, Lee and Suh 1998). A Cochrane registered systematic review by Whitehead and associates (Whitehead, Moss, Cardno and Lewis 2002) showed that add-on antidepressant therapy for schizophrenic patients with co-morbid depression may be of therapeutic value; yet, the presence of limitations such as a small number of trials, and possible publication bias required that their results be interpreted with care. A new quantitative review of seven trials (n=202) by Rummel and colleagues, showed that the combination of antipsychotic with antidepressant regimen may perhaps be effective in controlling predominant negative symptoms. However, they included 3 studies only with SSRIs, and so to draw a conclusion on the efficacy of SSRI add-on therapy would be premature. Furthermore, the authors assert that their findings require substantiation by further larger-sized trials (Rummel, Kissling and Leucht 2005).

Most of the previously mentioned studies include small sample sizes ranging from 20 to 75 patients (Silver and Nassar 1992; Buchanan, Kirkpatrick, Bryant, Ball and Breier 1996). To detect clinical improvement in psychiatric symptoms measured by positive and negative syndrome scale (PANSS) or brief psychiatric rating scale (BPRS), a 20% difference between groups is required, i.e. 150 participants per study arm (α= 0.05; power 85%)(Thornley and Adams 1998). To reach statistical power, we conducted a meta-analysis of studies assessing SSRI add-on therapy for the negative symptoms of schizophrenia. The results of this meta-analysis are of therapeutic importance, considering the chronic nature of negative symptoms; which may also shed light on the potential role of serotonin in the pathophysiology of negative symptoms.

Perspective neurobiologique

There is evidence for a cascade of events leading to the mechanism of action of SSRI add-on therapy for the negative symptoms. Negative symptoms are associated with abnormal structural changes in the brain (Miller and Tandon 2001). These changes may lead to alteration in the circuits involved in shifting motivation (Seeman 2001), inducing desensitization (reward system) (Bressan, R. A., Erlandsson, Jones, Mulligan, Flanagan, Ell, and Pilowsky 2003; Pycock, Kerwin, and Carter 1980), and ever-increasing degeneration (neuroplasticity) (Castner, Williams, and Goldman-Rakic 2000). Consequently, these lead to the imbalances of the neurotransmitters (chiefly dopamine and serotonin) and hormones (cortisol and pyridostigmine) (O'Keane, Abel, and Murray 1994; Saffer, Metcalfe, and Coppen 1985). Hence, by giving antipsychotics to these patients, clinicians hope to restore the balance, in the neurotransmitters and the hormones in the brain.

Persisting primary negative symptoms may require a second medication, antidepressant (SSRI) (Silver 2004). However, the mechanism by which the SSRI augmentation therapy affects the course of negative symptoms is still unknown; several neurobiological hypotheses are postulated below.

One of the main hypotheses lies in that antipsychotic combined with SSRIs may increase levels of dopamine and or neurepinephrine in the prefrontal cortex, resulting in an improved antidepressant response (Kapur and Seeman 2001). Specifically, this efficacy is

driven from enhancing the postsynaptic 5-HT1a mediated neurotransmission. Consequently, in order to comprehend the treatment approach to persisting negative symptoms, mechanism of action pertaining to antipsychotic and SSRI, the nature of the negative symptoms, and the underlying brain structures and circuit has to be understood.

Mécanisme d'action des antipsychotiques

When considering treatment models for schizophrenia, the role of dopamine receptor blockade and modulation remains dominant (Seeman and Kapur 2000). The optimal binding of dopamine D2 receptors is crucial to balancing efficacy and adverse effects. In other words, transient D2 receptor antagonism is sufficient to obtain an antipsychotic effect, while permanent D2 receptor antagonism increases the risk of adverse effects such as EPS (Stahl 2001a, 2001b). Partial D2 receptor agonists offer the possibility of maintaining optimal blockade and function of D2 receptors (Seeman and Kapur 1997). Balancing pre-synaptic and postsynaptic D2 receptor antagonism is another probable mechanism that can, through increased release of endogenous dopamine in the striatum, protect against excessive blockade of D2 receptors (Seeman, Wilson, Gmeier and Kapur 2006).

Antipsychotic effects on the negative symptoms of schizophrenia are postulated to relate to dopamine turnover in the prefrontal cortex. This can be modulated by combined D2 and serotoninergic 5-HT2A receptor antagonism, partial D2 receptor antagonism or the preferential blockade of inhibitory dopamine auto-receptors (Stahl 2000). This mechanism

of serotonergic modulation may be is associated with a beneficial increase in striatal dopamine release as observed in imaging studies (Dewey, Smith, Logan, Alexoff, Ding, King, Pappas, Brodie and Ashby 1995). This hypothesis is discussed in detail by Horacek and colleagues (Horacek, Bubenikova-Valesova, Kopecek, Palenicek, Dockery, Mohr and Hoschl 2006).

Mécanisme d'action des ISRS

SSRIs selectively targeting serotonin receptors were developed based on the hypothesis that alterations in receptor sensitivity may play a role in both the efficacy of antidepressant drugs and the pathophysiology of depressive-like symptoms (e.g., negative symptoms), (Feighner 1999). These agents, which include fluoxetine, paroxetine, sertraline, fluvoxamine, and citalopram, has shown higher efficacy to their older counterparts (MAOI, TCA) with a lesser side effect profile. The SSRI class of drugs has a wide range of clinical applications in the full spectrum of depressive disorders and in many other psychiatric disorders (Maina, Albert, Salvi and Bogetto 2004; Reist, Nakamura, Sagart, Sokolski and Fujimoto 2003).

Potent 5-HT2 blockers were seen to improve secondary negative symptoms by simply reducing the EPS. SSRI increases serotonin levels at the synapse stimulating a large number of serotonin receptors subtypes and perhaps with various interactions with dopamine receptors, which is postulate to be the underlying their antidepressant potential (Stahl 2000). Two mechanisms of action which are of interests in generating antidepressant

efficacy lies in, firstly that increased levels of serotonin occur after desensitization at the dendritic 5-HT1a receptor and terminal 5-HT1d receptor. Secondly, SSRIs may be are down-regulating postsynaptic 5-HT2a receptors (Berman, Sporn, Belanoff, Schatzberg and Charney 2004).

Base neurobiologique des symptômes négatifs

Burden of negative symptoms in schizophrenia is clinically associated from alogia (poverty of speech and its content; blocking; increased latency of response interest), avolition-apathy (impaired grooming and hygiene; lack of perseverance at work or school dependency on others to structure; physical anergia activities), anhedonia-asociality (decreased recreational interests and activities; decreased sexual interest and activity, decreased ability to feel intimacy, new experiences and closeness; decreased relationships with close and distant acquaintances), flat affect or blunting (monotonous facial expression associated with socialization, recreation, decreased spontaneous movement productivity, initiative, perseverance; paucity of expressive gestures and curiosity; poor eye contact; affective non-responsiveness; inappropriate affect; lack of vocal inflection positive and negative events), and attentional impairment (work inattentiveness; inattentiveness during mental status testing) (Sadock and Sadock 2003).

Structural changes are observed in schizophrenia patients with negative symptoms. These symptoms may be due to alterations in the micro circuitry in the brain, specifically the right insular region of the fronto-temporal region (Shin, Kwon, Ha, Park, Kim, Hong,

Moon, Lee, Kim, Kim and Chung 2006). Other studies report on various structural changes including 1) enlargement of the lateral ventricles (Andreasen 1982; Andreasen, Ehrhardt, Swayze, Alliger, Yuh, Cohen and Ziebell 1990a; Andreasen, Swayze, Flaum, Yates, Arndt and McChesney 1990b; Marks and Luchins 1990) 2) third ventricle, 3) smaller temporal lobe, 4) hippocampal, and superior temporal gyral volume (Flaum, O'Leary, Swayze, Miller, Arndt and Andreasen 1995). From a metabolic standpoint, these symptoms were reported to be negatively linked (decreased activation) with regional cerebral blood flow in the nucleus lenticularis, prefrontal cortex, and the temporal cortex (Andreasen, Rezai, Alliger, Swayze, Flaum, Kirchner, Cohen and O'Leary 1992). In tandem, Liddle and colleagues (Liddle, Friston, Frith, Hirsch, Jones and Frackowiak 1992) studied these symptoms under positron emission topography and found decrease in blood metabolism in the prefrontal and left parietal cortex and heighten activity in the caudate nuclei.

There is no evidence that damage to any one structure, pathway or region is uniquely responsible for producing negative symptoms. Instead, a network of cortical and sub-cortical areas is implicated, within which, damage, dysfunction or abnormal cerebral circulation, and neuronal metabolism lead to an increased probability of the incidence of these symptoms (Frith, Friston, Herold, Silbersweig, Fletcher, Cahill, Dolan, Frackowiak and Liddle 1995; Keightley, Seminowicz, Bagby, Costa, Fossati and Mayberg 2003). These connectivity theorists suggest that various elements are at play in the control of negative symptoms of schizophrenia including: 1) alteration in the motivation system (limbic-ventral-striatopallidal system) (Seeman 2001); 2) changes in the dopamine system (striato-

thalamo-cortical circuits) (Kane and McGlashan 1995); 3) degeneration of the ventral tegmental area (Castner, Williams and Goldman-Rakic 2000); 4) alteration in the reward system (mesolimbic) (Bressan, Erlandsson, Jones, Mulligan, Flanagan, Ell and Pilowsky 2003; Pycock, Kerwin and Carter 1980); 5) change in the cholinergic-dopaminergic system (Laruelle, D'Souza, Baldwin, Abi-Dargham, Kanes, Fingado, Seibyl, Zoghbi, Bowers, Jatlow, Charney and Innis 1997; Tandon and Greden 1989; Tandon, Shipley, Greden, Mann, Eisner and Goodson 1991); 6) Glutamate (cortico-cortical; cortical-basal ganglia and cortico-limbic) (Lahti, Holcomb, Medoff and Tamminga 1995). These systems are discussed by Brown and Pluck (Brown and Pluck 2000).

From a fundamental neuro-scientific point of view, Weinberger and Berman (Weinberger and Berman, 1996) suggest that these symptoms are associated with dopaminergic hypoactivity in the PFC. However, others report a correlation between increase in cerebral ventricular size and persisting negative symptoms (Potkin, Weinberger, Linnoila and Wyatt 1983). In the contrary, Pickar and group (Pickar, Breier, Hsiao, Doran, Wolkowitz, Pato, Konicki and Potter 1990a) found a lower concentration of 5-hydroxy indole acetic acid in schizophrenia patients. Therefore there is no clear consensus on the implication of change in the ventricular system and the negative symptoms.

Hence, one possible reason for this treatment approach is that, from a molecular view, dopaminergic and serotonergic systems interact in the PFC and endogenous 5-HT can enhance dopamine release in the nigro-striatal pathway (Pickar, Litman, Konicki, Wolkowitz and Breier 1990b; Yadid, Pacak, Kopin and Goldstein 1994), it is possible that,

when added to first generation antipsychotics, SSRI may increase dopamine levels in PFC, specifically, increasing extra-cellular fluid dopamine levels in the mPFC as seen in rodents (Csernansky, King, Faustman, Moses, Poscher and Faull 1990; Jibson and Tandon 1998; Meltzer 1989; Zhang, Perry, Wong, Potts, Bao, Tollefson and Bymaster 2000). However, with regards to second generation antipsychotics, although paradoxical, the serotonergic antagonism potential seems to be the key element (Meltzer 1992). The paradox lies in adding an SSRI, a serotonin agonist, to an antipsychotic with serotonin agonist properties. In addition, as to whether serotonin neurotransmission causes the negative symptoms, or negative symptoms are related to serotonin-dopamine interaction in the ventral tegmental area, remain another link to a difficult question. However, other neurotransmitter systems such as glutamatergice and cholinergic may be involved in inducing negative symptoms. Therefore, dopamine-serotonin interaction may only be part of a more complex system (Miller and Tandon 2001).

In conclusion, by blocking 5-HT2A and D2 receptors, a higher affinity for 5-HT2A receptors than for D2 receptors is created which leads to lower risk for EPS. Alternatively, 5-HT2A/D2 receptor antagonism increases the dopamine release to the PFC and striatum, and thus it becomes one of the therapeutic potential of the negative symptoms. This action is also valid for partial dopamine receptor agonist with 5-HT2A antagonism (such as aripiprazole), 5-HT1A receptor agonist and blockade of D2 receptors that increases dopamine release to the PFC, striatum and limbic structures. In addition, the blockade of 5-

HT2C receptors and blockade of D2 receptors acts in concert to block 5-HT2A receptors. Moreover, blockade of alpha-adrenoceptors and D2 receptors includes alpha1-adrenoceptor antagonism, decreases activity of serotonin projections, and in combination with D2 receptor blockade would mimic 5-HT2A/D2 receptor antagonism, which is Similar to alpha2-adrenoceptor (Horacek, Bubenikova-Valesova, Kopecek, Palenicek, Dockery, Mohr and Hoschl 2006).

Synthèse des études

This meta-analysis consists of eleven (N=11) robust clinical trials, included in our meta-analysis (Sepehry, Potvin, Elie and Stip 2007) table 1. Other researchers have reviewed this treatment approach on several occasions. Starting with Evins and Goff in 1996 (Evins 1996) who briefly addressed SSRI add-on treatment in their review paper on adjunctive antidepressant drug therapy for negative symptoms of schizophrenia. Sproule, et al in 1997 (Sproule, Naranjo, Brenmer and Hassan 1997) reviewed SSRI's pharmakodynamics on the Central Nervous System (CNS), and Zullino, et al (2002) (Zullino, Delacrausaz and Baumann 2002) investigated the status of SSRI add-on therapy approach in schizophrenia. A complete review consisting of the pharmacokinetics and pharmakodynamics of the SSRI add-on treatment was conducted by Henry Silver (Silver 2004). A recent systematic review on antidepressant add-on therapy for persisting negative symptoms has been carried out by Rummel and colleagues (Rummel, Kissling et al. 2005), showed that antidepressants in general were of potential benefit to schizophrenia patients. However, our result with 11 studies specific to SSRIs shows the contrary. Moreover, other studies were also published on the topic that we considered inconclusive regarding this treatment approach. Ultimately, these studies; case reports, open trials and cross-over designs were dropped out from our meta-analysis. The exclusion of the cross-over studies is discussed in our recent publication (Sepehry, et al 2007) and later in the discussion section. That leads us to the appraisal of few open trials, case reports, and two randomized, placebo-controlled studies, published after 2004. The randomized studies were one with fluvoxamine (Chaichan 2004) and the other with paroxetine (Jockers-Scherubl, Bauer,

Godemann, Reischies, Selig and Schlattmann 2005) as co-treatment for persisting negative symptoms.

The study by Chaichan (Chaichan 2004) was a short term 6-week trial that investigated the efficacy and adverse effects of fluvoxamine add-on to olanzapine compared to olanzapine alone, in twenty patients suffering from acute exacerbation of schizophrenia. They assessed efficacy with the Brief Psychiatric Rating Scale (BPRS) and side effects with the Udvalg for Kliniske Undersogelser (UKU) side-effect scale. They reported significant changes in the total means of BPRS and the general psychopathology score in the add-on treatment arm ($P = 0.037$ and $P = 0.045$, respectively). This study was excluded from our meta-analysis, given the fact that BPRS is not specifically designed to detect negative symptoms changes in patients suffering from schizophrenia. Nonetheless, authors suggested that their findings are of value, given the fact that in a combined treatment approach, the medication was well tolerated and more effective than monotherapy.

The second trial by Jockers-scherubl' group (Jockers-Scherubl, Bauer et al. 2005) was a double-blind, 12-week long-term study attempting to replicate their previous positive findings. They carried-out this trial with 30mg of paroxetine co-administered with antipsychotics, in comparison with a placebo group to treat negative symptoms in chronic schizophrenia patients (n=29), even though there is no definition of the criteria of chronicity in schizophrenia. The authors screened the patients using Positive and Negative Syndrome Scale (PANSS), and later with the Hamilton Depression Scale (HAM-D) and

scales for extrapyramidal side-effects. With close to 14 % attrition, they opted for an intention-to-treat (ITT) analysis based on the 25 patients who were present for at least one follow-up assessment, and analyzed their data by the mean of last observation carried forward (LOCF). With a fairly naturalistic method, they reported a decrease in PANSS-negative subscale mean score in both groups. This change was reported to be significant between groups (paroxetine vs. placebo) but the mean depression scores were almost constant. Nonetheless, they recommended use of paroxetine for treatment of negative symptoms in chronic schizophrenia.

Other studies of open trials were methodologically weaker (Silver, Kushnir and Kaplan 1996; Takahashi, Sugita, Higuchi and Shimizu 2002), as were case reports (Silver, Jahjah and Kushnir 1995; Silver, Kaplan and Jahjah 1995); and studies with mixed patient types (Bondolfi, Eap, Bertschy, Zullino, Vermeulen and Baumann 2002).

The case reports by Silver and colleagues were on fluvoxamine add-on treatment that led to modest clinical improvement, taking into consideration psychotic as well as negative symptoms. Furthermore, an open pilot study by Silver et al, with the same SSRI add-on medication, reported a decrease in negative symptoms score on SANS and so concluded that these agents may be potentially effective in the treatment of schizophrenia patients with persisting negative symptoms.

Bondolfi et al (Bondolfi, Eap et al. 2002) presented another open label short trial (during 30 days), showing the positive effect of fluoxetine combined therapy (20mg/day from day 6) in mixed type psychotic inpatients (e.g., schizophrenia, schizoaffective,

schizophreniform disorder) (N=11). They investigated pharmacokinetics and safety of this compound in combination to Risperidone (4 or 6 mg/day), and have assessed negative symptoms with PANSS-negative subscale. They reported 91% of their patients' demonstrated clinical improvement, defined as a reduction of 20% or more in symptoms and 70% on depressive like symptoms compared to the baseline. The depression symptoms were tested with Montgomery-Åsberg Depression Rating Scale (MADRS). Further, they noted non-significant change in severity and incidence of extrapyramidal symptoms, and adverse events, in the co-administration arm of their trial. This study was not included in our meta-analytic study because of mixed patient type.

Another open label trial, Takahashi et al. (Takahashi, Sugita et al. 2002), in a 12 week period, investigated the efficacy and safety of co-administration of fluvoxamine to risperidone for the treatment of residual positive and negative symptoms in chronic patients with schizophrenia (N=30). They had no attrition. They have evaluated symptoms with PANSS and extrapyramidal symptoms with Simpson-Angus extrapyramidal effects (S-A) scale. During the trial, they have observed no significant change in any PANSS sub-scales or in S-A scale of their patients, and so consequently concluded that fluvoxamine is ineffective as a co-treatment agent for chronic schizophrenia patients.

Although Kasckow and associates' study (Kasckow, Mohamed, Thallasinos, Carroll, Zisook and Jeste 2001) was published before 2004, it was missed from other reviews. This perhaps suggests to reviewers' potential bias. Kasckow and colleagues investigated citalopram (20-40 mg/day) add-on treatment over a 10 week single blind trail.

Their study included both middle-aged and elderly chronic schizophrenia patients (N=19, 9 were randomly assigned to the active treatment arm). The peculiarity to their study was that their sample consisted of some patients receiving typical (Haloperidol, Fluphenazine, Thioridazine) and some atypical (Olanzapine, Risperidone, and Quetiapine) antipsychotics. Patients were tested both at baseline and at the end of the trial with a 17-item Hamilton Rating scale for Depression (HAMD), for depressive symptoms and, PANSS and Clinical Global Impression (CGI) scale for general symptoms, however, the raw scores for PANSS were not provided in their study. The author reported amelioration in both positive and negative symptoms with no side effects; in addition, the active treatment arm demonstrated superior performance in HAMD and on CGI scale than the comparison group. The author reminded that their findings are only preliminary and further controlled trials are warranted. This study was also excluded from our meta-analysis for two reasons, first due to the fact that it was the only study explicitly stating that it was a single blind trial, and second, for including patients receiving both atypical and typical antipsychotics in the active treatment arm.

Méta-analyse et ISRS

There are inconsistencies in research results regarding the co-prescription of antipsychotics with SSRI. While some studies report positive results using poly-pharmacy, others report negative results.

The positive results that emerge from adjunctive conventional antipsychotics include the use of fluvoxamine (Silver and Nassar 1992; Silver and Shmugliakov 1998; Silver, Barash, Aharon, Kaplan and Poyurovsky 2000) and fluoxetine (Goff, Midha, Sarid-Segal, Hubbard and Amico 1995). The negative results on the other hand were obtained from the study of Arango and collaborators using various antidepressant (Arango, Kirkpatrick and Buchanan 2000) and Buchanan and colleagues (Buchanan, Kirkpatrick et al. 1996) using fluoxetine, Lee (Lee, Kim et al. 1998) using serteraline, and Salokangas and coworkers (Salokangas, Saarijarvi, Taiminen, Kallioniemi, Lehto, Niemi, Tuominen, Ahola and Syvalahti 1996) using citalopram. Simply evaluating the possibilities among random and double blind studies, fluvoxamine tends to produce more positive result than the other antidepressants when given with conventional antipsychotics. All of the studies evaluated negative symptoms of schizophrenia ranged from short to medium-term treatment duration (e.g., 2 to 12 weeks).

Studies with various range of treatment duration provided different conclusions [refer to Szegedi, Anghelescu, Wiesner, Schlegel, Weigmann, Hartter, Hiemke and Wetzel 1999; Hiemke, Peled, Jabarin, Hadjez, Weigmann, Hartter, Modai, Ritsner and Silver 2002]. One of the limitations of these studies was insufficient sample size, which renders generalization difficult, hence lowers the statistical power (Buchanan, Kirkpatrick et al.

1996; Hiemke, Peled et al. 2002; Takahashi, Sugita et al. 2002). Usages of other drugs such as, anticonvulsant, lithium, or anticholinergic, in cases of parkinsonism-like symptoms were not fully reported.

Most studies use clozapine with adjuvant antidepressant treatment. It is believed that clozapine is used mostly in cases of patients that are "chronic" as well as unresponsive to other atypical antipsychotics. There are limited reports of comparison groups in those studies to placebo (refer to Buchanan, Kirkpatrick et al. 1996; Kasckow, Mohamed et al. 2001). Buchanan and group (1996), and Kasckow and colleagues (2001) final observation of, a non significant negative symptoms improvement, is unreliable due to the testing variability (e.g., BPRS, PANSS, & SANS). One question comes to light, and that is, how significant is "clinically significant" for these patients suffering from a disproportionate amount of disability. Although, these symptom groupings have been integrated initially as a norm for diagnosis of schizophrenia in the DSM-IV (Keefe and McEvoy 2001), most of the studies have had DSM-III-Revised as their diagnostic base, which demonstrate that the idea of adjunct SSRI antidepressant to antipsychotic treatment is an old unresolved issue.

Other factors to consider include the mental state (e.g., chronic or non-responsiveness) of the patients that has not been fully reported. Another significant factor that has been neglected is the relevance of age and duration of illness correlated to symptoms improvement. Furthermore, the link between negative symptoms to positive, cognitive or affective symptoms has not been fully investigated. Kibel and colleagues

(Kibel, Laffont and Liddle 1993) denote a correlation between negative symptoms and cognitive deficits.

Méta-analyse

Qu'est-ce-qu 'une méta-analyse?

Meta-analysis allows data to be collapsed so that generalization can be made. Meta-analysis is a quantitative approach using statistical analysis on a collection of individual independent studies. Thus, in this manuscript we tend to answer to the following questions: 1) Why did we do a meta-analysis? 2) How did we apply meta-analytic technics? 3) What answer do we have? 4) What is the significance of our findings?

> "Meta-analysis refers to the analysis of analyses. I use it to refer to the statistical analysis of a large collection of results from individual studies for the purpose of integrating the findings. It connotes a rigorous alternative to the casual, normative discussions of research studies which typify our attempts to make sense of the rapidly expanding research literature" (Glass 1976).

In today's language, meta-analysis is considered a new method, a sophisticated more objective method than systematic reviews (Glass 1976). The only difference between these methods is that a meta-analysis consists of mathematical analysis of the data (published or unpublished) that aggregate findings to a common metrics (notably called: effect size, effect estimate, or magnitude of treatment effect), allowing the comparison of multiple outcomes. The effect size is the strength or the magnitude of the relationship, or the degree of departure from the null hypothesis (Rosenthal and Rosnow 1991). Thus, a biger effect can be either interpreted as good outcome to a treatment strategy, or the

contrary. Yet, meta-analysis is the foundation to decision analysis, which provides data in order to evaluate cost effectiveness of different strategies in treatment or approaches (Byers and Stullenbarger 2003). In brief, meta-analysis may consist of the amalgamation of a minimum of 2 research studies/trials collected, coded, and interpreted using statistical methods similar to those used in primary data analysis. Noteworthy, meta-analysis based on two research studies can give rise to further discussions. For instance, in terms of treatment for the common cold, a meta-analysis based on 2-studies can be considered misleading, whereas in for a severe illness, such as malignant glioma with a low prevalence, it can be permissible. Therefore, one must be vigilant in interpreting the results of a given meta-analysis. The results obtained from the meta-analysis are summaries (re-evaluation) of studies and exploration of relationships, thus, the meta-analysis is more objective and exact compared to a narrative review, with which authors provide a sequence of chronological discourse on previous findings (Greenhalgh 1997). By pooling the studies in the meta-analysis, we increase the power by reducing standard error of the effect size, followed by a shrinking of the confidence interval around the effect estimate which in turn increases the likelihood of detection of a non-zero population effect. It is noteworthy that a small confidence interval elevates the precision of the effect estimate. However, this is relative as to whether random or fixed effect models are used (which we will discuss later), since each model is sensitive for specific questions under investigation (Cohn and Becker 2003). Meta-analysis is known to be an aid to medical and social sciences for decision making purposes, resolving conflicting evidence, answering questions where the answer is

uncertain, explaining variability in practice or simply to confirm the appropriateness of current practice (Higgins and Green 2005). Others note that meta-analysis bridges research to clinical practice (Byers and Stullenbarger 2003).

A good meta-analysis notes of a clear objective necessity and consists of focused and sophisticated research trials, while investigating differences in existing studies. It is also important to remember that the obtained results are provisional, representing the best evidence at the time meta-analysis was conducted, and that these results are subject to change in time as more studies are conducted (Mulrow and Lohr 2001). Predominantly, the quality of a meta-analysis is only of use and appreciated as the individual studies on which it is based. For instance, if the meta-analysis consists of at least one weak study (e.g., open label as opposed to RCT), the result is affected. The result of any given study affects the result of the meta-analysis. Therefore, even if the meta-analysis is well performed on poor data, it will still result in a poor outcome. In short, in writing a meta-analytic review, simplicity is the key. The following section introduces the meta-analysis method.

Advant propos

As stated by O'Rourke (O'Rourke 2006), it appears that the first meta-analysis was performed by a British statistician, Karl Pearson in early 1900's. Pearson (Pearson 1904) performed this meta-analysis in order to overcome the problem of reduced statistical power in studies with small sample sizes. By 1932, the statistical procedure for integration of research was followed by Fisher (Fisher 1932) and Bridge (Bridge 1932).

The first medically associated meta-analysis was published in 1955. Some years later, in the 1970s, a more sophisticated statistical analysis was introduced in educational research, initiated by Gene V Glass, an American social scientist. The Oxford English dictionary lists the first usage of the term in the statistical context as of 1976. Later, the term was interchangeably used with "validity generalization" (Schmidt and Hunter 1977). The statistics pertaining to meta-analysis was further expanded by Larry V. Hedges and Ingram Olkin, and so was the beginning of this concatenating enterprise (Hedges 1983). At that time, flaws in meta-analysis were detected (Cooper and Rosenthal 1980). It was then in 1984 that the future of this versatile and useful approach to scientific research became mainstream (Green and Hall 1984). Today, as it was predicted, the literature associated with meta-analysis is expanding (Rosenthal 1991). Meta-analytic studies were first key-worded as meta-analysis in 1977 (Guzzo, Jackson et al. 1987). Meta-analysis was introduced in PubMed in 1989. This research approach is some times called, analysis of the analyses (Glass 2000), systematic renews, quantitative synthesis, statistical research integration, a retrospective look at the data, or testing relationships that had never been examined by the primary researcher (Cooper and Hedges 1994). Egger and Smith states, that no other term is appropriate than "meta" as other terms are interchangeably used in representing other types of findings, or they are not robust at all. For instance, "overview" is used for traditional reviews, and "pooling" incorrectly implies that the source data are merged (Egger and Smith 1997). However, the actual term, meta-analysis was first suggested by Michael Scriven's meta-evaluation (evaluation of evaluations) in 1969

(Stufflebeam 2001). So today, the term "validity generalization" no longer implies to meta-analysis but to a special application of meta-analysis. Additional developments led to the establishment of the Cochrane collaboration (http://www.cochrane.org/) in 1992 for health care system (Egger and Smith 1997; Geddes, Freemantle, Streiner and Yarnolds 1998), and in 2000 the international Campbell Collaboration (http://www.campbellcollaboration.org/) for social, behavioral, and educational arena. These organizations both carry an online library that creates a high-standard in conducting meta-analysis studies available for use by clinicians and the general population. In many fields, meta-analysis is well accepted as the preferred methodology for summarizing literature. Today, according to Ceballos and colleagues (Ceballos, Garcia-Campayo, Artal and Valdizan 2001) psychiatry is the medical specialty in which more studies on meta-analysis have been carried out. Consequently, their impact on clinical practice is scarce, or in other words, no evidence-based approach is at its infancy. To help in sound clinical practice, and provide better decision making with regards to symptom control and functioning enhancement, meta-analysis of negative symptoms with uncontrolled outcomes has lead to greater power detective of effects. In schizophrenia research in particular, the heterogeneity of symptoms, variance in assessment, and differences in treatment approach, make results difficult to generalize.

Principes fondamentaux de méta-analyse et de statistiques

In a given amassed set of studies, the number of trials with a low sample size (e.g., ranging between 20 and 75 total enrolled research subjects) with minimal precision and

power to increase the applicability of the findings, is problematic. Although we have mentioned before, it is of value to repeat this notion in this context. By aggregating the sample size of the clinical trial studies in the meta-analysis, we increase the power by reducing standard error of the effect size, followed by the shrinking of the confidence interval around the effect estimate which in turn, increases the likelihood of the detection of a non-zero population effect (Hedges and Vevea 1998). It is noteworthy to realize that, small confidence intervals elevate the precision of the effect estimate. However, this is relative to whether the random or fixed effect model is used, because each model is sensitive for specific question under investigation (Cohn and Becker 2003).

Compared to literature reviews, meta-analysis is more accurate and less subjective; and in comparison to smaller studies, in which the role of risks can not be detected, meta-analysis can point to them.

Méthodes de méta-analyse

There are 3 major approaches to meta-analysis: 1) vote counting or binary outcome, 2) combining significance levels, and 3) combining estimate of effect sizes.

The first approach, using the non-parametric statistics (e.g., odd-ratio (OR), relative risk (RR)) has several limitations (Gurevitch and Hedges 1999). First, it may fail to identify a true treatment effect that may be important clinically; second, it considers every study equally, no matter of the sample size; third, it does not provide with a useful estimate of the magnitude of an effect across a group of studies (Freemantle and Geddes 1998).

The second method, combining the significant effect has its own limitations. Initially, important data such as mean, standard deviation, and the sample size that are used as the raw data are missed. Then, the reported significant level is an estimate that does not take the sample size in to consideration. Therefore, the weighting of the effects would be inappropriate. Furthermore, combining the effect estimate per study would not give a precision on the strength or weakness of the effect obtained, particularly in cases of variability and weight of studies. Another caveat to this method is that in cases of non-significant results in many studies, the degree of significance is not reported, which leads to publication bias. This notion will be discussed later.

In this manuscript we elaborate notably on the third statistical method, the combining of the effect estimate, mainly using parametric tests such as Cohen's *d* or Pearson's r. This last approach which was developed by Glass et al (Glass, McGaw and Smith 1981) and Hunter et al (Hunter, Schmidt and Jackson 1982), to this day, is regularly used. Qualitative steps required for a meta-analytic approach such as collecting and classifying data (coding), before implementing meta-analytic data-analysis and interpretation are noted in the following sections.

In every meta-analysis, the investigator starts with summarizing the data for each study and computes the effect size. For example, if a study reports means and standard deviations, one computes the standardized mean difference and the variance for each effect size.

Stratégies de recherche

In a given meta-analysis, several search strategies are of importance; notably, searches of the electronic engines (e.g., PubMed, PsychINFO, Excerpta Medica dataBase (EMBASE)) on various platforms (e.g., OVID), which is then enhanced by hand searches (journal by journal, conference proceedings, and cross-referencing with other reviews and reference lists) (Pai, McCulloch, Gorman, Pai, Enanoria, Kennedy, Tharyan and Colford 2004). In regard to clinical trials, pharmaceutical companies are also contacted in order to collect the unpublished data. It is imperative to note, that this approach in later years would be less implemented by the advent of the new development in registering clinical trials, since clinical trials registration ameliorates access to unpublished data. It is noteworthy that, in the awareness of missing data, in the emerging studies, authors can be contacted to collect further pertinent information. These methods are used in order to gather maximum data to rule out a decision, based on minimal prejudice, and high sensitivity and specificity (McManus, Wilson, Delaney, Fitzmaurice, Hyde, Tobias, Jowett and Hobbs 1998).

Recherche par voie électronique

Starting with the relevant search engines, meta-analytic authors will use key words specific to the meta-analysis' question. The key words are usually generated by the expert in the field, and are usually descriptive of the type of the people (healthy or ill), type of the treatment or intervention (psychological or medical), and type of the effect of interest. These keywords are sometimes extensively expanded through usage of a thesaurus, usually

provided at each search engine. In the context of psychiatric and mental illness combined with pharmaceutical treatment, PubMed, PsychINFO, EMBASE, Cochrane trial register, Australasian medical index, and Current Content are usually investigated. This approach is not inclusive, and may contain a selection of other search engines. It is believed that there is a 30 to 70% overlap between databases (Dickersin, Scherer and Lefebvre 1994); hence, an organized in-house database cleared of the overlaps is a must. It is crucial to specify that the next section, hand-searching, is time consuming. Notably, few published meta-analysis follow this rule or report such performance. For instance, Guzzo and colleagues report that the electronic or computer searches are of convenience and are frequently understood to be more exhaustive than manual search, and have the potential to be exceedingly reliable (Guzzo, Jackson et al. 1987). It is important to know that, simply relying on abstract reviewing, as they are the first to be collected via electronic engines, would raise the chance of failing to collect important studies that would have been otherwise detected via reviewing of full articles (Potvin, Sepehry and Stip 2007).

Recherche manuelle

In order to gather the maximum number of studies (Dickersin, Scherer et al. 1994), journal by journal searches, cross-referencing, or by the mean of snowball procedure (Mullen 2003; Davis 2004) searching each article's reference list should be undertaken. Precisely, manual searching should be undertaken by covering gray literature (unpublished and difficult to retrieve studies, for instance dissertation abstracts or reference proceedings), thus controlling for the file drawer effect. Hand searching, in addition to searching

electronic databases, for instance Medline, has been reported to be of higher efficacy (Hopewell, Clarke, Lusher, Lefebvre and Westby 2002). For example, with regards to schizophrenia, peer reviewed journals such as *Schizophrenia Research* and *Schizophrenia Bulletin* are the main journals that usually meta-analytic authors tend to use to conduct a hand-search. Another method used to conduct a hand search is by considering the high frequency of the occurrence of a given journal in the database, in order to be used for this procedure. One example for utilization of this method is in the meta-analysis of the effect of antipsychotic medication on long-term memory published in *Journal of Psychopharmacology* (Thornton, Van Snellenberg, Sepehry and Honer 2006). The cross-referencing is usually carried-out with published reviews, including references listed at the end of each article.

Codage

The coding is a method to categorize studies with a set of a priori selected criteria, and hypotheses. This is to either systematically shrink (collapse) or lump together the gathered literature. The coding is used to delineate the types of research that are most appropriate to answer a particular question (Mulrow and Lohr 2001). This method is usually carried-out in collaboration with the authors to avoid all preconceived notions (biases) in study selection, and to diminish inter-rater and intra-rater disagreement. The coding is also used in order to assess the quality of research studies. A coding sheet or coding book usually accompanies the data/results (Brown, Upchurch, Anding, Winter and Ramirez 1996; Potvin, Sepehry and Stip 2006) (refer to the Appendix section). Sometimes

this is omitted, because of low number of studies enrolled in the meta-analysis. The coding is used precisely to determine which variable(s) has a moderating effect on the primary effect estimate, and enhances strategies for better research design (Brown, Upchurch and Acton 2003). In coding, pre-determined inclusion and exclusion criteria are set, and later, the studies are ranked based on their particularity, or on an in-house coding form. Each coding method may consist of categories pertaining to methodology (e.g., washout, baseline, end-point), study design (e.g., random, double blind, parallel controlled arm design), intervention description (e.g., type of antipsychotics: typical or atypical), and outcome measures (e.g., PANSS or SANS or Scale for the Assessment of Positive Symptoms -SAPS).

It is important to make a reference to the pooling versus combining in meta-analysis. The simple pooling of data is used to provide an overall summary of subgroup data or data from a number of related studies, which pay no attention to the distinctiveness of the sub-groups or individuals (Bravata and Olkin 2001). The combining of the data on the other hand, is used to put together subgroups or individual studies after they are being weighted.

Critères d'exclusion & d'inclusion

The criteria are adapted, specifically, to the clinical and research question which can be revised accordingly (e.g., if too few or too many studies are obtained, provided that care is taken to avoid making changes that would introduce bias). These criteria usually consist

of characteristics such as age, gender, population of study, and intervention of interest (SSRI add-on treatment for instance), then further limited to the language of the studies (e.g., English or French for instance). These standards are used to simplify identification of cognate studies that are consistent to the investigated hypothesis. The decision on exclusion and inclusion of studies is usually taken independently with two or more authors in order to decrease the likelihood of an occurrence of an error. If the decision among authors is not concordant, a consensus must be reached before any analysis is undertaken.

A good example of exclusion criteria is the relevance of population of study. Authors aim at weeding out articles that are not pertinent to the original question of study. For example, authors searching schizophrenia studies can limit select studies to patients suffering from schizophrenia and reject studies with patients suffering from schizophrenia-like symptoms. For instance, in our published study, the randomness, blindness of the participant and investigator, and the experimental design were the factors of interests.

Biais de publication

The basic concern with publication bias may results from unpublished data. Studies that report relatively large treatment effects are more likely to be submitted and/or accepted by the journals than studies which report more modest treatment effects. On the other hand, smaller studies get the chance to be put at display in the conferences, so, it is the responsibility of the meta-analyst to in corporate studies from numerous sources other than journal articles alone. Since the treatment effect estimated from a biased collection of

studies would tend to overestimate the true treatment effect (committing either of type I or II error), it is important to assess the liable extent of the bias, which has a great potential to impact on the conclusions and statistically threat the validity (Moller and Jennions 2001). Some of the possible biases in a given meta-analysis, for instance, are sampling, selection, and within study bias (Gallus and Leandro 2005).

Évaluation de la qualité des études

Quality assessment in meta-analysis is important. This is because we aggregate multiple trials that don't have common hypotheses in mind, or are conducted in different countries, have differing protocol, or ethical requirement. To be more specific, we have to conduct quality assessment of the trials to minimize impartiality in conducting the quantitative systematic review, gain insight into potential comparison, and guide interpretation of the findings. Although interpretation of the findings has to be limited – simply to report on what the literature says, and not what it may suggest – there are meta-analytic studies that fail to follow this golden rule. There are several factors that warrant quality assessment, for instance, including applicability of the findings (external validity), validity of studies, and trial designs characteristics (e.g., random vs. non-random) all of which affect the interpretation of the results. To date, there are more than 25 scales proposed for quality assessment of clinical trials (Moher, Jadad, Nichol, Penman, Tugwell and Walsh 1995; Moher, Jadad and Tugwell 1996). Some good examples would be scales developed by Jaded, et al (Jadad, Moore, Carroll, Jenkinson, Reynolds, Gavaghan and McQuay 1996), Cochrane for trial design assessment, or Chalmers and colleagues (Chalmers, Smith, Blackburn, Silverman, Schroeder, Reitman and Ambroz 1981). It is noteworthy that only Jadad and colleagues' scale is scientifically validated (Verhagen, de Vet, de Bie, Boers and van den Brandt 2001).

"Funnel plot"

Publication and other forms of selection favoritisms pose a threat to the validity of meta-analysis; hence, several methods to investigate this issue are undertaken. For instance, Funnel plot which, first was introduced by Light and Pillemer (Light and Pillemer 1984), is meant to detect such biases (Egger, Davey Smith, Schneider and Minder 1997). It is noted by Begg and Berlin (Begg and Berlin 1988) that funnel plot is the preferred informal mechanism for recognizing these types of biases. Funnel plot (scatter plot) is graphed by scheming of the trial-specific effect versus a measure of its precision. Presence of asymmetry in the plot suggests for prevalence of biases, or systematic dissimilarities between smaller and larger studies (Tang and Liu 2000). On the other hand, the non-biased structure of the plot is a point which is symmetrically scattered around the omnibus effect in the shape of an inverted funnel (Egger, Smith, Schneider and Minder 1997). And so, in the absence of bias, effect estimate from small size trials will scatter widely at the bottom of the graph, with the spread narrowing among larger studies (Stern and Harbord 2004).

In general, the funnel plot is a graphic representation of a measure of study size (usually standard error or precision) on the vertical axis as a function of effect estimate on the horizontal axis. Usually, bigger trials appear near the top of the graph, and tend to cluster closer to the mean effect size. Smaller size trials appear toward the bottom of the graph, and (given that there is greater sampling variation in effect size estimates of the smaller size trials), these effect sizes are expected to be dispersed across a range of values.

"Fail-safe N"

The classic fail-Safe N and the Orwin fail-safe N (Orwin 1983) procedures were developed to ask if we need to be concerned with the yielded effect estimate that may perhaps be an artifact of bias. The issues with publication bias lies in the ground that possibly a quantity of non-significant studies are missing from our omnibus analysis and that these studies, if included, would change the observed effect. Rosenthal (Rosenthal 1979) suggests that, we ought to compute the number of studies that would be required to nullify (changing in the opposite direction) the effect. If this number is relatively small, then there is undeniable foundation for concern. However, if this number is large enough (although subjective, relative to the total number of trials included); we can be confident that the yielded effect, while possibly inflated by the exclusion of some trials, is nevertheless not zero. What's more is that he also suggested this analysis be called a 'file-drawer' analysis, given the fact that file drawers being the alleged location of the missing studies. Later, Cooper proposed 'Fail-Safe N' as a term referencing to the number of missing studies/trials that would void the effect (Cooper 1979).

This approach has limitations (Hsu 2002). Initially, it presumes that the effect estimate in the hidden studies is zero, rather than considering the probability that a quantity of the studies/trials may well provide an effect estimate in the opposite direction. Accordingly, the number of trials essential to make this effect useless, the yielded effect estimate may be far smaller than the suggested Fail-Safe N. Also, this approach concentrates simply on statistical rather than clinical significance. That is, it possibly

provides us with the chance to emphasize that the yielded treatment effect is not zero, but it does not address the question of whether in light of clinical investigation, it remains clinically important after the omitted trials have been incorporated. In addition, although, the notion of small and large is very subjective, and there is no consensus in the literature on the numbers included in each category, there are meta-analyses using this conventional fail-safe method. We can nevertheless note that the fail-safe N algorithm is based on computation of p-value for each study, and their summation. On the contrary, the commonly established method, computes an effect size for each study, combines the effect sizes, and then computes the p-value for the combined effect. The two methods, the classical fail safe and omnibus effect estimate calculation, do not normally yield matching results. Whereby, total abandonment of the technique in favor of the more optimal methods, such as Orwin fail-safe N, Duval and Tweedie's Trim and Fill, etc, is suggested.

Like the classic fail-safe N, the Orwin fail-safe N addresses the likelihood that studies are omitted from the analysis and that these studies, if included in the analysis, would shift the effect size toward the zero effect. Yet, it is different from the classic method in several ways. First, the mean standard differences in means in the new studies (missing) can be a value other than zero; and second, the criterion value is an effect size estimate as opposed to p-value. That is, the Orwin fail-safe N is the number of (missing) studies that, when incorporated in the analysis, will shift the combined standard difference in means, past a specified threshold, notably selected by the investigator. This method is sounder, in the context of clinical investigation, the author-clinician is able to determine to what degree

treatment is effective (provides with room for personal maneuver), although the yielded effect estimate is close to zero.

Further mathematical methods are also available that are not in the scope of this manuscript to carry on an elaborative discussion. For instance, for advance mathematical techniques, a reference to Egger's Test of the Intercept (linear regression analysis) (Egger, Smith et al. 1997; Schulze, Holling and Bohning 2003), or Begg and Mazumdar Rank Correlation Test (Begg and Mazumdar 1994; Song, Khan, Dinnes and Sutton 2002), or Trim and fill by Duval and Tweedie (Duval and Tweedie 2000; Duval and Tweedie 2000) can be suggested.

Réduction des données

There are two methods in using key words, to either broadly or narrowly investigate the literature. These methods are also called the lumping or splitting. Each has its advantages and nuisances. The advantages of the lumping (broadly) are first to avoid duplication and second it is informative compared to the other method. Its disadvantages are feasibility (time consuming), its compromised complexity, and sometimes mixing apples with oranges. On the other hand, the splitting (narrowing) method is easily conducted and easily read, yet it is less informative and needs multiple reviews, which limit generalization. A good example of this is in pursuing a meta-analysis on the cytokines, investigating a single cytokine (e.g., IL-6), versus covering a majority of them (e.g., IL-2, IL-6, IL8, IL-10, etc).

Calculs méta-analytiques

Type de données

The two main types of data are dichotomous and continuous. In this manuscript, we discuss the latter. Other data types are ordinal data, counts and rates, and time to event data. For further elaborate explanation to this datum's usage in meta-analysis, a reference can be made to Cochrane's handbook (Higgins and Green 2005).

Statistiques paramétriques – non-paramétriques

Effect estimates can be calculated with several types of data from studies (explained in the above section), providing with parametric, or the non-parametric type statistics. It is noteworthy that there are mathematical formulas and tables available which will transform the odd-ratio to standardized mean difference (SMD) (or Hedges'g) and vice versa. SMD is equal to the square roots of 3 divided by π, multiplied by the log of odd-ratio. This helps the meta-analyst to pool both types of data. It is of essential value to note that, although pooling dichotomous data with continuous data is feasible, one must take into consideration the hypothesis in investigation, and thus mixing apples with oranges may have to be limited to particular issues.

The parametric statistic includes statistical data such as standard deviation. In other words, we take into account the statistical error in their mathematical formula when investigating a certain parameter. The best continuous data for calculating an ES are the original individual patients' data, yet, mean, and standard deviation along with sample size of the groups are highly valuable and regularly used. Good examples of such statistics are

mean changes, analysis of variance (ANOVA) with single degree of freedom, or student's t-test. These methods are usually used in the presence of normal data distribution. These types of data are also categorized as continuous type data, for instance, scores on a depression scale such as beck depression inventory or Scale for the Assessment of Negative Symptoms.

The non-parametric statistics are frequently used when the data is not equally distributed, and is usually with smaller sample size. One good example of such statistical method is the Mann-Whitney U test or its equivalence, the Wilcoxon rank sum test, where the statistical finding relies on the mode (ranking) rather than the median or the mean. This category of statistical method pertains to dichotomous data (binary or categorical) (for instance, "Yes or No" outcome, as antipsychotic resistant or no resistant). Other examples are OR, RR, or risk difference (RD).

Mesures de la taille de l'effet (2 groupes indépendants)

Différences normalisées entre deux groupes*

The weighted difference of the mean is calculated by the following formula:

$$\textbf{(1)}\ [d = M_1 - M_2 / \sigma\ ]$$

Where $[\sigma = \sqrt{[\sum(X - M)^2 / N]}]$; and where, X is the raw score, σ is the standard deviation of a population, $\sum$ is the sum, M is the mean, and N is the number of cases.

* For mathematical explanation on how the formulas are driven, please refer to Rosenthal (Rosenthal 1991)

Cohen defined *d* (a descriptive measure) as the difference between the means, ($Mean_1$ - $Mean_2$) or in the clinical trials ($time_1$- $time_2$, or treatment-placebo, experimental - control groups), divided by standard deviation (SD) of either group (Cohen 1988). Cohen argued that the standard deviation of either group could be used in the calculation when the variances of the two groups are homogeneous.

By convention the subtraction, $Mean_1$ - $Mean_2$, is prepared so that the difference is positive if it is in the direction of amelioration of the symptoms or in the predicted direction, and negative if in the direction of deterioration or opposite to the predicted direction.

However, in practice, the pooled standard deviation, σ_{pooled}, is commonly used (Rosnow and Rosenthal 1996), hence the following formula:

$$(2)\quad [d = M_1 - M_2 / \sigma_{pooled}]$$

$$\text{Where } [\sigma_{pooled} = \sqrt{[(\sigma_1^2 + \sigma_2^2) / 2]} \text{ and Power is } (\delta = d\sqrt{N/2})$$

Where, the pooled standard deviation is calculated through the square root of the mean square of the two errors (standard deviations) (experimental and control) (Cohen 1988). That is, the pooled standard deviation is the square root of the average of the squared standard deviations (formula #2). It is important to note that, for similar standard deviations, the root of mean square will not fluctuate substantially by simply averaging of the two variances.

Nonetheless, *effect estimate (Cohen's d)* can also be computed from the value from a *t*-test (Rosenthal and Rosnow 1991) or an F with 1 degree of freedom.

(3) $[d = 2t / \sqrt{(df)}]$ or $[d = t(n_1 + n_2) / [\sqrt{(df)}\sqrt{(n_1 n_2)}]]$

In the presence of equal patients or participants, the formula without the n's should be implemented. So the following formula is developed in cases of differing n's. In the equation # 3, the degrees of freedom for the *t*-test, is abbreviated as "df", and "n" for the number of cases (patients or participants) for each grouping.

However, Hunter and Schmidt (Hunter and Schmidt 1990) proposed, in the existence of equal sample size, utilization of pooled within-group SD provides with lesser sampling error than the control SD. They also provide with correction of the effect size for measurement error, by the suggesting the following corrective method:

(4) [Measurement error correction= $(ES/ \sqrt{r})$].

Cohen's *d* can be subsequently computed from r, the ES correlation with the succeeding formula:

(5) $[d = 2r / \sqrt{(1 - r^2)}]$

This effect size *(d)* can be computed from Hedges' *g* with the following formula:

(6) $[d = g\sqrt{(N/df)}]$

Hedges' *g*, another method to calculate the effect size, is an inferential measure. It is normally calculated by using the square root of the mean square error from the analysis of variance testing for differences between the two groups. Hedges' *g* is named after Gene V. Glass, one of the pioneers of meta-analysis.

(7) $[g = Mean_1 - Mean_2 / S_{pooled}]$

Where $[S = \sqrt{[\Sigma(X - M)^2 / N-1]}]$ and $[S_{pooled} = \sqrt{MSwithin}]$

Hedges' *g* also can be calculated from *t*-test results, investigating differences between the two groups (Rosenthal and Rosnow 1991). The formula with separate n's should be used when the n's are not equal. Yet, t^2 is equal to F when df equal 1 in the numerator of F.

(8) Independent *t*-test: $[g = t\sqrt{(n_1 + n_2)} / \sqrt{(n_1 n_2)}]$
or $[g = 2t / \sqrt{N}]$
or Two-group one way ANOVA: $[g=\sqrt{F}\ (n_1 + n_2)/ \sqrt{(n_1 n_2)}]$

The pooled standard deviation (σ_{pooled}) can be computed from the unbiased estimator of the pooled population value of the standard deviation (SD_{pooled}) and vice versa (Rosnow and Rosenthal 1996).

(9) $[\sigma_{pooled} = SD_{pooled} \sqrt{(df / N)}]$

Where df = the degrees of freedom for the MS error, and N = the total number of cases.

In addition, Hedges' *g* can be computed from r (the ES correlation) with the following formula:

(10) $[g = [r / \sqrt{(1 - r^2)}] / \sqrt{[df(n_1 + n_2) / (n_1 n_2)]}]$

Glass's delta is another method to compute effect sizes; it is defined as the mean difference between the experimental and control group divided by the standard deviation of the control group.

(11) $[\text{delta} = \text{Mean}_1 - \text{Mean}_2 / \sigma_{\text{control}}]$

In the case of missing effect estimate and presence of significance test value, the effect size can be calculated (Rosenthal and DiMatteo 2001).

(12) [significance test=effect size x study size].

Mesures de corrélation de la taille de l'effet « r »

Correlation measures of effect size r (ES correlation) can be obtained from the *t*-test value with the following formula:

$$\textbf{(13)}\ [r = \sqrt{(t^2 / t^2 + df)}]$$

Furthermore, the ES correlation can be calculated from a single degree of freedom; *F*-test value (e.g., a one way analysis of variance with two groups) with the following recipe

$$\textbf{(14)}\ [r = \sqrt{[F(1,\_) / (F(1,\_) + df\,\text{error})]}]$$

Where, the empty (_) spaces are for the other number (numerator), in degree of freedom associated with ANOVA.

The ES correlation can also be estimated via utilization of Cohen's *d* or Hedges' *g*:

$$\textbf{(15)}\ [r = d / \sqrt{(d^2 + 4)}]$$

$$\textbf{(16)}\ [r = \sqrt{\{(g^2 n_1 n_2) / [g^2 n_1 n_2 + (n_1 + n_2) df]\}}]$$

And it can be converted to *d* and vice versa:

$$\textbf{(17)}\ [d = 2r / (\sqrt{1 - r^2})]^*$$

Les modèles: fixe et aléatoire (hiérarchique)

Test of heterogeneity (e.g., *Q*-test) in meta-analysis recurrently lacks statistical power (The test of heterogeneity is explained later under heterogeneity sub-heading). This

* In the meta-analytic studies, *r*'s are typically presented rather than r^2

lack of power is important specifically in the terms of significant heterogeneity. Different methods are invented so to facilitate investigation of this variability among studies.

The fixed effects model developed by Mantel and Haenszel (Mantel and Haenszel 1959) presumes that there is a distinct fundamental population treatment outcome, which will be echoed most accurately by larger size trials with greater statistical power. Fixed effects models may unjustly domineer over important differences between study effects.

However, the random effects model (DerSimonian and Laird 1986), on the other hand, assumes that the trials are investigating different, hitherto related, treatment results, and taking into perspective the variability among studies. This is so, for both the effect size estimates and in the distance between the lower and upper tails of the confidence interval (Schulze, Holling et al. 2003). This model is considered as flexible, for example, in the case of no heterogeneity (p-value of 0.5 or greater), it acts as fixed effects model; however, when the p-value shortens, it increasingly takes this into account. Moreover, the random effects model increases the weight of smaller studies that are prone to the systematic bias.

The choice between models remains controversial, although there are reviews on the topic reporting that both avoid controversy particularly when they give the same answer (Freemantle and Geddes 1998). The random effect model is used principally in the case of unexplainable heterogeneity (Higgins and Green 2005).

Intervalle de Confiance (CI)

The confidence interval is the mathematical representation of the variation. It is the degree to which the true effect sizes differ across studies. It is calculated as the addition of sampling error variation with the true variation. The wider the CI (distance between lower tail and upper tail), the less accurate is the measured effect estimate, in other words, the greater the sampling variability. As a result, interval estimates are sometimes omitted which according to Steiger and Fouladi is a sign of embarrassment (Steiger and Fouladi 1997). In existence of heterogeneity, CI is wider when the random effect model is used, and on the contrary, in the absence of heterogeneity, both models should provide exactly the same CI values.

Report of CI (upper limit and lower limit) in the meta-analytic manuscripts, which has its limitations as well as its strengths (Cumming and Finch 2001), and it is encouraged by the Cochrane. This strength relies on quick elucidation of the results, encourages meta-analytic thinking, and provides with further information on the precision of the effect estimate. Furthermore, the poor overlaps of the CI for the results of individual studies, usually signals the presence of statistical heterogeneity. Its weakness lies on its potential contribution on the true alpha, the probability of a type I error (May 2003).

Mathematical usage of the CI for means is in the unavailability of the standard deviation in the studies:

(18) [SD= $\sqrt{N}$ x (upper limit- lower limit)/ 3.92]

In the case of large sample size (N>60) at 95% confidence level; 3.92 is the 2 time 1.96 standard errors for 2 tails. And for smaller sample size, a reference to t-distribution values table is necessary to replace the 3.92.

Hétérogénéité

Factors leading to heterogeneity can be split into three categories, the clinical, the statistical, and the methodological. The clinical heterogeneity is frequently based on patient selection, baseline disease severity, techniques utilized, outcomes, and duration of follow-up. The methodological heterogeneity on the other hand, consists of, randomness in design, patient withdrawals, and LOCF (Thompson 1994). The statistical heterogeneity is due to variability between continuous type data set (e.g., ANOVA vs. mean and SD). We can confirm the presence of heterogeneity in two ways. A common way of indicating the extent of heterogeneity is by a statistical test, which is described as Cochran's $\chi 2$ test or the Q-test. Another way is the graphical approach (discussed under representation of findings). The mathematical formula investigating inconsistency following a Q-test is the I^2:

(19) $I^2=[(Q-df) / Q,]*100$

A value superior to 50% obtained from this formula signals a substantial diversity/variability in effect estimate of the trials (Higgins, Thompson, Deeks and Altman 2003).

The Q-statistic (or Q-test) is a mathematical test that assesses whether the effects produced by a group of studies varies primarily because of sampling error or represents systematic differences among the studies in addition to sampling error. A non-significant Q indicates possible homogeneity of the effect and a significant point to the heterogeneity of the effect (at the 0.05 level or less). If the effect produced by a group of studies is found to be homogeneous, then the studies are considered to be from the same population (e.g., schizophrenia) and the analysis of the group mean effect is warranted. On the contrary, it can be explained that there is a possibility that our group contains two or more distinct sub-populations of studies (e.g., investigating schizophrenia patient with primary persisting negative symptoms vs. secondary negative symptoms). These studies should be further subdivided into other categories of variables (e.g., primary or secondary negative symptoms) to identify these sub-populations and achieve homogeneity within each group. Q-statistic is useful for model testing (fixed or random); in other words, to confirm or reject the model chosen by the meta-analyst provides a good fit for the obtained data. Establishing homogeneity always comes before analysis and interpretation of the group means. It is not atypical to fail at obtaining homogeneity in some or all study groupings. In such cases, the meta-analyst cannot make confident interpretations regarding which variables or factors are contributing to the obtained findings (Grimm and Yarnold 1997).

Significance in Q-test is defined *a priori* as $p < 0.1$ (Song, Sheldon, Sutton, Abrams and Jones 2001). This test for heterogeneity is considered to have low statistical power (Gavaghan, Moore and McQuay 2000), when trials have small sample sizes or are few in

number. This explains that although a statistically significant result may indicate a probable heterogeneity, a non-significant result must not be taken as evidence for lack of heterogeneity. This is also why a p-value of 0.10 (a more liberal criterion) is more acceptable, than the conventional level of 0.05. When there are many studies in a given meta-analysis, the test has high power to detect a small amount of heterogeneity that may be clinically trivial (Higgins, Thompson et al. 2003). Thus, it is prudent for a distinguished meta-analyst to use equally heterogeneity assessment as well as qualitative evaluation of the combinability of the studies.

Méta-Régression

Correlations linking categorical altercating variables to ES, from time to time, provide us with potential associations that are especially useful to our understanding of a given question. In other words, a meta-regression graph or analysis helps in assessing the relationship between study results and study characteristics (Guzzo, Jackson et al. 1987). Therefore, meta-regression facilitates further formulation of potential causal inferences and strives for understanding of assorted results. Examination of moderating variables (e.g., in our case, type of antipsychotic used, dosage of medications, type of scale, etc.) via meta-regression analysis adds to theory development and increases the richness of empirical work.

However, Cochrane discourages usability of this method in meta-analysis involving less than 10 studies.

Présentation des résultats

When the meta-analytic procedures are complete, it is important to present the information in the fashion that is easily accessible and easy to follow. This can be done through multiple venues. We must report the number of included and excluded studies. For the included studies, a brief report explaining the design, giving information on the number of subjects enrolled, the type of the setting, intervention, outcome measures, outcome, and demographic information can be granted. Later, for the excluded studies, descriptive information is desirable. In order to describe this section, one can include variables such as the state of the articles (e.g., ongoing studies, etc) (Higgins and Green 2005). A clear table separating the excluded from the included studies would be an asset. However, the number of studies retained from the searches can be presented in a fashion recommended by the Lancet, starting from searches of the search engines leading to exclusion and finally the number of studies retained for the purpose of meta-analysis (Moher, Cook, Eastwood, Olkin, Rennie and Stroup 1999) (refer to appendix section).

Further, studies included in the meta-analysis with their associated effect estimate, sample size, p-value, and confidence level (usually set at 95%) aside to a blobbogram are used to graphically show the impact of the overall effect. Depending on the software used and preference of the authors, the variances as well as the z-value are also reported. It is noteworthy that, the interpretation of the variance is the same as the CI.

"Blobbogram"

The Blobbogram is a graphical representation of the studies included in the overall meta-analysis. It consists of horizontal lines, diamonds, black 'blob' and lozenge(s) associated with effect estimate that shows how well the treatment did compared to the control, for example. The blobbogram facilitates the interpretation of data, and compares studies side-by-side. Hitherto, its use is to detect bias in meta-analysis. One example of this kind of graph is what we have achieved in our meta-analysis, provided in the figure 1, where each horizontal line represents a different comparison (often time, individual trials).

Other types of graphs are Radial Plot and/or Funnel plot, Galbraith Plot (Galbraith 1988; Galbraith 1994), Abbe Plot (Song 1999), Thompson sensitivity Plot, Bayesian Shrinkage plot, and Cumulative plot (Lau, Antman, Jimenez-Silva, Kupelnick, Mosteller and Chalmers 1992). Examples of this graphical representation are provided in a study by Pai and colleagues (Pai, McCulloch et al. 2004). However, there exists other methods to represent the effect estimate, for instance one can refer to Stem and Leaf display, which has no graphical interface (Rosenthal 1995). For instance, the Forest plot shows the information from the individual studies at a glance (e.g., amount of variation between studies and an estimate of the overall result) (Lewis and Clarke 2001).

In meta-analysis, we must note that graphs are also adapted in the interpretation of data and investigating heterogeneity (Baujat, Mahe, Pignon and Hill 2002).

Interprétation des résultats

To interpret the findings, meta-analysts refer to the rule-of-thumb by Cohen. Cohen summarizes effect sizes of continuous data into 3 groups: 1) small if the effect is less than 0.20; 2) medium if near 0.50; 3) and large if it is equal or bigger than 0.80. This categorization differs for the correlation coefficient or odd-ratio effect estimates. For the correlation coefficient, the effect size estimate is considered small if it is 0.10 or lower, medium if it is near 0.25, and large if it is equal or larger than 0.40. For odd-ratio, it is considered small if it is equal or less than 1.50; medium if it is around 2.50 and large if it is equal to or higher than 4.30. It is noteworthy that this arbitrary classification corresponds to the distribution of effects across meta-analyses amassed by Lipsey and Wilson (Lipsey and Wilson 1993). Also, it is important to mention that this method of interpretation has its own limitation, for instance, it does not take into account the context of the intervention. For example, a small effect may be consequential if the intervention is for severe and a fairly intractable illness such as for cancer. Furthermore, the yielded omnibus effect estimate can be translated into a percentage in order to demonstrate the possible effect of the treatment or treatment strategy. For the conversion table of the effect estimates to percentage, a reference to the article by Freemantle and Geddes (Freemantle and Geddes 1998), or Zakzanis (Zakzanis 2001) can be made.

"Comprehensive Meta-Analysis"

Comprehensive meta-analysis (CMA) software (http://www.meta-analysis.com/) was developed by a team of experts in meta-analysis both in United States and United Kingdome. During our study of meta-analytic approach on the add-on treatment of SSRI to antipsychotics in schizophrenia, we have been observant of advantages of CMA, for instance it includes a wide array of sophisticated options for data entry, analysis, display, structure, and data manipulation.

Résultats

Caractéristiques des études

Five hundred ninety-one (591) possible articles emerged from our search. 552 studies were rejected based on the evaluation of the abstract and 28 studies on the evaluation of the article, based on:

(i) Type of studies (e.g. reviews, case studies, challenge studies, surveys, retrospective studies, open-label trials, post mortem studies, molecular studies, letter-to-the-editor, book chapter, and cross-over studies);

(ii) Type of population (e.g. non-human subjects, patients with comorbid conditions, non-schizophrenia patients);

(iii) Treatment type (e.g. non-SSRI antidepressants, non-pharmacological therapy);

(iv) Complete unavailable data (Salokangas, Saarijarvi, Taiminen, Kallioniemi, Lehto, Niemi, Tuominen, Ahola, and Syvalahti 1996; Poyurovsky, Pashinian, Gil-Ad, Maayan, Schneidman, Fuchs and Weizman 2002; Bustillo, Lauriello, Parker, Hammond, Rowland, Bogenschutz and Keith 2003).

The remaining 11 studies which responded to our inclusion criteria (data was available for each study) were clinically heterogeneous (Table 1), in terms of: (i) SSRI medication: fluoxetine (5 studies), fluvoxamine (2 studies), sertraline (2 studies), citalopram (1 study), and paroxetine (1 study); (ii) antipsychotic drug: atypical (3 studies), typical (5 studies), not specified (1 study) and mixed (2 studies); (iii) psychiatric assessment: SANS (7 studies) and PANSS-N (4 studies) (Note: Studies

were classified according to population description explicitly stated by authors); (iv) patient type: chronic (7 studies) and non-chronic (4 studies); (v) psychiatric setting: inpatient (5 studies) and outpatient (6 studies); (vi) treatment duration: from 4 weeks to 4 months; (vii) type of data: LOCF or ITT (4 studies) versus study completers (7 studies).

Two studies, first, Poyurovsky, et al (2002) and second, Bustillo and colleagues (2003) were not primarily designed to assess negative symptoms. Three studies were using previously published data; hence, they were ignored from analysis (Taiminen, Syvalahti, Saarijarvi, Niemi, Lehto, Ahola and Salokangas 1997; Silver, Aharon and Kaplan 2003; Silver, Nassar, Aharon and Kaplan 2003) (refer to table 1).

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Table 1. Study characteristics.

Studies*	N	SSRI	SSRI-Dosage (mg/day)	Antipsychotic	Scales	PT	EPS/ Depression controlled	TX-Duration (weeks)
Silver & Nassar (1992)	30	Fluvoxamine	50-100	Un-specified	SANS	Chronic / Inpatients	Yes/Yes	5
Buchanan et al (1996)	33	Fluoxetine	20-80	Clozapine	SANS	Not- responder/ Outpatients	No/Yes	8
Spina et al (1994)	30	Fluoxetine	20	Typical	SANS	Chronic/ Inpatients	**/Yes	12
Arango et al (2000)	32	Fluoxetine	20	Typical	SANS	Outpatients	Yes/Yes	8
Silver et al (2000)	52	Fluvoxamine	50-100	Typical	SANS	Chronic/ Inpatients	Yes/Yes	6
Lee et al (1998)	36	Sertraline	50	Typical	PANSS-N	Chronic/ Inpatients	Yes/Yes	8
Poyurovsky et al (2002)	24	Fluoxetine	20	Olanzapine	SANS	1st episode/ Inpatients	No/Yes	8
Bustillo et al (2003)	20	Fluoxetine	20-60	Olanzapine	PANSS-N	Outpatients	Yes/Yes	16
Salokangas et al (1996)	75	Citalopram	20-40	Typical	PANSS-N	Chronic/ Outpatients	**/No	12
Mulholland et al (2003)	20	Sertraline	50-100	Mixed	SANS	Chronic/ Outpatients	**/Yes	4
Jockers et al (2005)	25	Paroxetine	20-30	Mixed	PANSS-N	Chronic/ Outpatients	**/Yes	12

PT=patients; TX=treatment; In=Inpatients; **=no data.

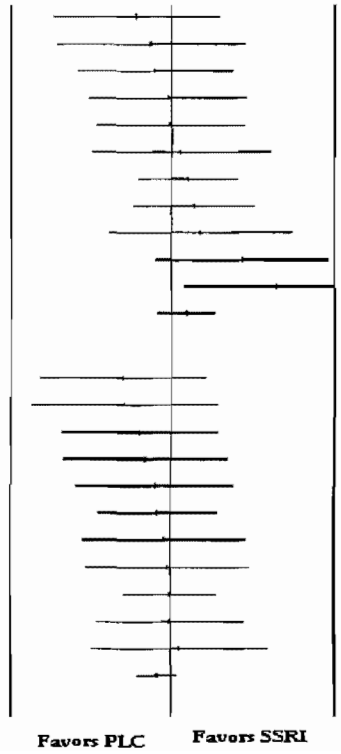
* References are marked with an asterisk (*) in the bibliographic section.

Synthèse quantitative des données

Eleven randomized, double blind, placebo-controlled trials, with parallel arm design (N= 393 patients at end-point) were identified in which add-on SSRI therapy was compared to antipsychotic monotherapy. Using end-point (end of trials) data, no significant differences were observed between the treatment groups for negative symptoms (standardized mean difference Hedges's g= 0.178; p= 0.191; random-effect model), yet it was slightly heterogeneous (Q= 16.83; p= 0.078). An overall 5% attrition has been calculated (refer to Figure 1). Interestingly, for baseline data, a composite effect size estimate for negative symptoms was obtained, boarder on significance (N= 412; standardized mean difference = -0.179; p= 0.072), suggesting a potential study bias. No significant differences were detected at baseline between the SSRI and placebo groups for age, sex, positive, depressive and EPS,

Figure 1. SSRI add-on therapy for negative symptoms of schizophrenia

	Folowup	Citation	EffectName	SSRI	NTotal	Effect	PValue
	After	Bustillo	PANSS	Fluoxetine	30	-,443	,223
	After	Poyurovsky	SANS	Fluoxetine	24	-,262	,514
	After	Buchanan	SANS	Fluoxetine	33	-,214	,534
	After	Arango	SANS	Fluoxetine	32	-,053	,880
	After	Lee	PANSS	Sertraline	36	-,016	,961
	After	Mulholand	SANS	Sertraline	26	,103	,788
	After	Salokangas	PANSS	Citalopram	75	,204	,376
	After	Silver 2000	SANS	Fluvoxamine	52	,280	,314
	After	Jockers	PANSS	Paroxetin	25	,349	,380
	After	Silver & Nassar	SANS	Fluvoxamine	30	,864	,022
	After	Spina	SANS	Fluoxetine	30	1,278	,001
Random	**After (11)**				**393**	**,178**	**,191**
	Before	Bustillo	PANSS	Fluoxetine	30	-,606	,099
	Before	Jockers	PANSS	Paroxetin	25	-,586	,147
	Before	Buchanan	SANS	Fluoxetine	33	-,405	,244
	Before	Silver & Nassar	SANS	Fluvoxamine	30	-,328	,364
	Before	Arango	SANS	Fluoxetine	32	-,195	,575
	Before	Silver 2000	SANS	Fluvoxamine	53	-,170	,537
	Before	Spina	SANS	Fluoxetine	30	-,088	,806
	Before	Poyurovsky	SANS	Fluoxetine	30	-,051	,888
	Before	Salokangas	PANSS	Citalopram	87	-,023	,913
	Before	Lee	PANSS	Sertraline	36	-,016	,962
	Before	Mulholland	SANS	Sertraline	26	,101	,792
Random	**Before (11)**				**412**	**-,179**	**,072**



Controlling for the masked effects, secondary analyses were performed. Standardized mean differences for negative symptoms were calculated for the following categories: antipsychotic type (typical, atypical or mixed), SSRI medication (fluoxetine), psychiatric setting (in/outpatient), psychiatric assessment (PANSS-N & SANS) and treatment duration (more or less than 12 weeks). It is noteworthy that Evins and Goff (1996) recommend a period of no less than 12 weeks for polypharmacy with add-on SSRI of negative symptoms. A non-significant composite standardized mean difference was reached for all of the secondary analyses performed.

A run was also carried excluding Bustillo and colleagues (2003) and Poyurovsky et al (2002). A low and significant effect size for negative symptoms was reached (N= 339; Hedges's g= 0.277; CI= -0.087 to 0.640; p= 0.049) and homogeneous (Q= 12.312; p= 0.138). Additionally, when studies were divided based on severity of illness (chronic / non-chronic), a moderate effect size for negative symptoms was obtained for the chronic group of studies (N= 274; Hedges's g= 0.386; CI= -0.018 to 0.791; p= 0.014), and so the composite effect estimate was no longer heterogeneous (Q= 9.060; p= 0.170). When studies were separated into LOCF or ITT versus study completers, similar results were yielded. Effect estimates were non-significant and small: LOCF or ITT [ES=0.093; P-value=0.594] and study completers [ES=0.240; P-value=0.225].

Sensitivity analysis has been performed in order to control for the methodological limitations (end-point heterogeneity & *baseline* differences in negative symptoms). This has been carried out based on the mean values reported by different researchers. Mean values were transformed into Z-scores using their standard deviations for assessing a pooled variance (refer to Table 2). The new data were then analyzed for differences

between the two study conditions (SSRI vs. PLC) and between initial scores and final appraisal with a 2x2 factorial ANOVA. The critical level of significance was set at 5%. Patients improved in time (F= 21.94, df =1, 40, p<0.001) but no differences observed between the two medication regimen (F = 2.64, *df* =1, 40, p=0.112 ns). Same method was replicated for the so-called "chronic patients", again time-treatment interaction emerged to be non-significant (F= 0.88; *df* =1, 24; p=0.357).

Table 2. Z-scores obtained for each study.

Studies*	Baseline		End-point	
	Placebo	*Add-on SSRI*	*Placebo*	*Add-on SSRI*
	Z_1	Z_2	Z_3	Z_4
Buchanan et al (1996)	-0,2465	0,1661	-0,0991	0,1219
Spina et al (1994)	0,4650	0,5421	0,1908	-1,2916
Arango et al (2000)	-0,1817	0,0260	0,0519	0,1038
Silver et al (2000)	-0,0622	0,0895	0,1513	-0,1632
Silver & Nassar (1992)	0,6276	1,0015	-0,4254	-1,2037
Poyurovsky et al (2002)	0,7726	0,8178	-1,1366	-0,8255
Mulholland et al (2003)	0,0880	-0,0176	0,0176	-0,0880
Salokangas et al (1996)	0,3939	0,4166	-0,3676	-0,5802
Lee et al (1998)	-0,0246	-0,0082	0,0082	0,0246
Bustillo et al (2003)	-0,2367	0,3836	-0,3020	0,1551
Jockers et al (2005)	0,3811	0,8675	-0,4104	-0,8302

* References are marked with an asterisk (*) in the bibliographic section.

Discussion

The aim of our meta-analytic investigation was to question the effect of treatment with SSRI add-on therapy for burden of negative symptoms. Our meta-analysis provides no clear evidence for the polypharmacy with SSRI for negative symptoms of schizophrenia based on the following reasons. First, there is lack of statistical significance in the composite effect estimate at end-point, comparing SSRI add-on to antipsychotic monotherapy. Also, this effect remains non-significant even when baseline data is compared with end-point. Second, the lack of efficacy is not attributable to clinical factors such as age, sex, and positive, depressive or extrapyramidal symptoms, or any of the potential confounding factors such as psychiatric setting and assessment, type of antipsychotic, and specific type of SSRI. Our result is in concord with the newly developed collaborative consensus statement on negative symptoms by National Institute of Mental Health and Measurement and Treatment Research to Improve Cognition in Schizophrenia (NIMH-MATRICS) (Kirkpatrick, Fenton, Carpenter and Marder 2006).

The challenges in pursuing this meta-analysis are discussed in the form of questions and answers. These questions and answers can be categorized as, methodological variability, neuropharmacological likelihood explanation, and clinical perspective. Furthermore, we have provided some possible explanations to the results that we have obtained.

Aspect méthodologique

Questions which surfaced were the following:

1- Why was the end-of study scores used instead of assessment of change? Why have we not considered using mean changes to calculate effect size estimates?

Although we have considered this approach, this method was abandoned, because it would not have allowed identifying the potential study bias (in this case, barely significant) that we found when we compared baseline negative symptoms between the two groups (SSRI vs. placebo).

2- Why were cross-over studies excluded from the meta-analysis?

We preferred not to include these studies, mainly for two reasons. First, we kept the methodological homogeneity in our meta-analytic evaluation. Second, we also had other methodological reasons to rule them out. There were three cross-over studies: Vartiainen, et al. (Vartiainen, Tiihonen, Putkonen, Koponen, Virkkunen, Hakola and Lehto 1995); Brancato, et al. (Brancato, Barbini, Regazzetti, Colombo and Smeraldi 1994); and Friedman, et al. (Friedman, Ocampo, Elbaz, Parrella, White, Bowler, Davis and Harvey 2005). In the case of the Vartiainen, et al. 1995 study, BPRS was used for symptom evaluation. As for the Friedman, et al 2005 study, the study was not designed to primarily assess negative symptoms. Nonetheless, cross-over design has other problems, such as carry over (a type of period-by-intervention interaction), and the risk of drop-out due to longer duration compared to parallel group trials. In addition,

meta-analytic techniques, particularly of the statistical type, are limited when adding cross-over studies to parallel arm trials.

Based on the low number of included studies (N=11), this would limit the power of detecting heterogeneity; however, there should have been very large differences between studies if it were detected.

3- Why was the investigation of heterogeneity not explained explicitly?

As recommended in the literature (Glasziou and Sanders 2002), in order to address the heterogeneity problem, we performed the following sub-analyses (masking effects), controlling for:

(i) the type of scale used (PANSS-N & SANS);

(ii) psychiatric setting (in/outpatients);

(iii) duration of treatment;

(iv) SSRI medication (fluoxetine);

(v) the type of antipsychotic (typical, atypical or mixed).

All of the above mentioned sub-analyses provided non-significant effect estimates. Furthermore sub-analysis separating the studies by the state of the illness 'chronicity' showed that the effect size was no longer heterogeneous. The benefit of our meta-analysis is that all our analyses were calculated using random effect model. This model adjusts for heterogeneity among the effect size estimates, as it allows the study outcomes to vary in a normal distribution between studies.

Also, since the majority of our studies included 20 to 75 subjects, we used Hedges' *g* as opposed to Cohen's *d*, which takes into account the variability in sample sizes.

Another serious concern that one can bring to light has to do with the way we have accounted for attrition. It appears that only RCT completers were included in our analyses. Such a method can be seen as even more flawed than the somewhat undesirable Last Observation Carried Forward. Moreover, it can be said that the results of our analyses tend to be biased and have very limited generalizability; hence, we reason by the following position: this selection method noted in the data extraction of the manuscript was chosen to keep high number of patients (observed cases). Statistically, the use of LOCF or ITT by itself would lead to biased results and the true alpha may exceed the pre-given alpha. Yet, we have used both types of data (LOCF or ITT, and full data without attrition) in our analysis so to be closer to real-life situation. However, the sub-analysis of studies by separating them into LOCF or ITT and RCT completers groups has yielded similar results. Both effect-estimates were non-significant and small.

4- What role did the length of the studies in affecting the results have?

It is of our interest to note that 3 out of the 4 studies which pertained "chronic" patients – were observed to be, possibly the responding subgroup. This leads to the question of whether the important relevant 'chronicity' was of the patients' conditions or of the additive treatment employed. This would appear to be a significant caveat in the non-finding of a therapeutic effect to additive SSRI pharmacotherapy for negative symptoms in patients suffering from

schizophrenia. An attempt at separating the studies by "chronicity" was appealing. However, we did not follow this approach as it could have been misleading given the fact that the terminology regarding "chronic" group was not clear (Lesage and Morissette 2002). Also, by dividing the group considered as non-chronic based on study length, we would have had only 3 studies of short duration. These 3 studies comprise one study where negative symptoms were not the primary variables (weight gain was their primary variable). In addition, the non-chronic category pertained also to studies that were not explicitly asserting the state of the illness.

Aspect clinique

Two clinical questions arose. First, why was Obsessive Compulsive Disorder (OCD) one of the criteria of exclusion, even if the patient met all the other inclusion criteria? Initially, according to Berman and colleagues (Berman, Chang and Klegon 1999), this subtype of schizophrenia patients have distinct pathophysiology, treatment response, and clinical course. For instance, these schizophrenia patients have a poorer prognosis. Subsequently, by excluding comorbid OCD, we have insured patient homogeneity.

Second, why was there a discrepancy when the inclusion criterion shows "schizophrenia spectrum disorder" where the whole rest of the paper is written as if it is about schizophrenia? In response, all of the studies included in this meta-analysis involved schizophrenia, with the exception of the Bustillo study (Bustillo, Lauriello, Parker,

Hammond, Rowland, Bogenschutz and Keith 2003), which involved both schizophrenia and schizoaffective patients. Then again, in this study, negative symptoms were not the primary variables of investigation. As a reminder, we carried out a sub-analysis by removing studies which were not designed to primarily assess negative symptoms.

Aspect neuropharmacologique

Our results are of relevance to the neuropharmacology of antipsychotic medications. One possible rationalization to our yielded effect estimate would be through the neurobiological alterations. According to both animal and human data, a dopaminergic hypoactivity in the medial prefrontal cortex (mPFC) seems to underscore the negative symptoms of schizophrenia (Grace 1993; Finlay 2001). In this vein, the efficacy of second-generation antipsychotics in the treatment of negative symptoms has been attributed to their ability to modulate prefrontal dopaminergic activity. In animals, second-generation antipsychotic drugs have been shown to increase dopamine release in the mPFC (Heidbreder, Foxton, Cilia, Hughes, Shah, Atkins, Hunter, Hagan and Jones 2001; Westerink, Kawahara, De Boer, Geels, De Vries, Wikstrom, Van Kalkeren, Van Vliet, Kruse and Long 2001; Ichikawa, Li, Dai and Meltzer 2002). Similarly, brain imaging studies have shown a (partial) prefrontal restoration in schizophrenia patients during treatment with second-generation antipsychotics (Honey, Bullmore, Soni, Varatheesan, Williams and Sharma 1999; Stip, Fahim, Mancini-Marie, Bentaleb, Mensour, Mendrek and Beauregard 2005). This prefrontal restoration could be related to the 5-HT_{2A}/D_2 ratio of

affinities of second-generation antipsychotics. With the exception of amisulpride (Meltzer, Li, Kaneda and Ichikawa 2003), second-generation antipsychotics have greater affinity for serotonin 5-HT_{2A} receptors than they do for D_2-dopamine receptors, which is not the case for any first-generation antipsychotic drug (Meltzer, Matsubara and Lee 1989). In animals, serotonin and dopamine exert antagonist actions (Kostrzewa, Reader and Descarries 1998). By blocking serotonin receptors, atypical antipsychotics would disinhibit dopaminergic neurons in the PFC (Kapur and Remington 1996). As such $5HT_{2A}$ antagonists (e.g. ritanserin) have little effect on dopamine release in any brain region. However, when they are combined with a selective D_2/D_3 antagonist (e.g. raclopride), 5-HT_{2A} antagonists facilitate dopamine release in the prefrontal cortex (Andersson, Nomikos, Marcus, Hertel, Mathe and Svensson 1995; Westerink, Kawahara et al. 2001). In this very context, some authors have noticed that the use of SSRI medication for negative symptoms appears somewhat paradoxical (Silver 2004). How could indirect serotonin receptor agonists such as SSRI relieve negative symptoms when serotonin receptor antagonists such as second-generation antipsychotics are thought to do so? However, actually, from a psychopharmacological perspective, inhibiting the re-uptake of serotonin and blocking the 5-HT_{2A} receptors might not be a real paradox: 5-HT_{2A} and $5HT_{21A}$ receptors are strongly associated with each other and the 5-HT_{2A} blockade could induce its anti-negative/anti-depressive effects presumably by an indirect activation of 5-HT_{1A} receptors. SSRIs inhibit the re-uptake of serotonin, leading to an increased serotonin level, which acts at 5-HT_{1A}

receptors. It's therefore a synergistic mode of action. Insofar as SSRI add-on therapy does not relieve negative symptoms, there might simply be no paradox.

Yet again, SSRI medications are indirect agonists at 5-HT_{1A} receptors, which also modulate dopaminergic transmission. 5-HT_{1A} and 5-HT_{2A} receptors have opposed neurochemical and behavioral effects (Marek, Carpenter, McDougle and Price 2003; Celada, Puig, Amargos-Bosch, Adell and Artigas 2004). For instance, 5-HT_{1A} receptor agonists can stimulate the release of dopamine in the PFC (Ichikawa and Meltzer 1999). In the current context, it can thus be argued that augmentation of antipsychotic therapy with SSRI (which are indirect 5-HT_{1A} agonists) may increase dopamine release in the PFC, therefore providing an additional relief of negative symptoms.

In short, by aggregating small numbers of available studies (N=11), and considering the above mentioned question and answers, our meta-analysis showed no evidence of an effect for treating negative symptoms in schizophrenia. This would lead us to opt for other strategic methods such as, biopsychosocial approach, which is also recommended by the recent Canadian clinical practice guidelines (2005) for treatment of schizophrenia.

With insignificant change in this symptoms during add-on therapy, the guideline recommends to re-evaluate diagnosis, to increase the dosage in cases of multiple-episode patients, and in case of lower side-effects, to maintain observation of these patients with uninterrupted combination therapy for longer than 8 months. Therefore, further clinical placebo controlled, randomized trials with higher enrolled number of patients with

concurrent consideration of the guideline is warranted. Additionally, with regards to categorization approach to diagnosis of schizophrenia, the literature emerging from our systematic review teaches us to find a precise and clear definition for classification, i.e., chronicity, and negative symptoms. Henceforth; we must incorporate this new terminology into our new trials.

Nevertheless, the result of the current meta-analysis facilitates not only for the clinical scientist, but also for physician in order to minimize trial and error when co-prescribing SSRI's for management of schizophrenia persisting negative symptoms. Although our result failed to provide heightened evidence for this combination therapy for multiple-episode schizophrenia patients, it may provide insight into pharmaco-genetic approach by helping to design safer and more efficient drugs.

Conclusion

The main purpose of this meta-analysis was to put ample evidence in simple comprehensive form, in order for clinician and researchers to integrate the new findings as part of there clinical examination and to use as a guideline. Thus our meta-analysis was produced out of necessity, to aggregate constructive information, from the cryptic data, abbreviated in journals and other documents (printed or non-printed)(Glass 2000).

With the experience of carrying out other meta-analysis (Thornton, Van Snellenberg et al. 2006), extensively investigating the literature on the method and the laws associated with this approach, and taking into account what has been accomplished by the Cochrane group, this work can be summarized as the following:

Meta-analytic approach helps to address some of the challenges in psychiatric research. For instance, in the existence of multiple answers to a given question, which prevent us from solemnly relying on the significance tests of a few or solitary result as an appraisal of its worth. Also, it assists us in apprehending recurring outcomes with the matching trend. Thus meta-analysis consists of multiple studies, even in the presence of a non-significant result, which is more influential to the evidence than a single significant result or non-systematic reviews. This last notion is subjective. For instance, a study with presence of high number of subjects may precisely provide with ample power to reach a generalizable conclusion, such is the case with Schizophrenia Outpatient Health Outcomes (SOHO) study (Novick, Bousono, Suarez, Olivares, Montejo, Haro, Edgell and Ratcliffe 2005).

In the completed meta-analysis, owing to the availability of data both for baseline and end-point of trials, we have performed a more robust statistical procedure to detect apparent sampling bias. An orthogonal 2 by 2 factorial analysis of variance was performed. In order to carry out this analysis, we have first transformed all the reported mean, standard deviations and n's per each arm of the study to a standardized Z score. Then the Z-scores were used in the ANOVA. This article is the first meta-analysis that has demonstrated the marriage of significance test with effect size to investigate time treatment interaction effect; thus detecting sampling bias.

In general, meta-analysis has certain caveats (Rosenthal and DiMatteo 2001). Meta-analysis shares the same disadvantage as traditional, non-quantitative, narrative reviews of the literature. Its strength lies in, recognizing the background in a given domain; keeping the statistical significance in perspective; limiting wasted data; asking for more focused research questions; and finding moderating variables. In perspective, our meta-analytic investigation provides research-clinicians with knowledge on the appropriateness of current practice-polypharmacy-for the treatment of negative symptoms in schizophrenia by understanding the best current evidence, eleven randomized controlled trials.

The above article is an example of meta-analysis performed on continuous data. It provides with answers to some of the clinical concerns in clinical psychiatry with regards to decision making for better treatment planning in schizophrenia research and guidance for future search. In other words, this meta-analysis integrated medical professionals' expertise with aggregating evidence, consequently helping clinician to make sound conscientious,

explicit, and judicious decision pertaining to treatment regimen of patients suffering from negative symptoms in schizophrenia with SSRI co-administration.

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Appendices (Annexes)

Directive pour la recherche des données :

QUOROM statement flow diagram (Moher, Cook et al. 1999).

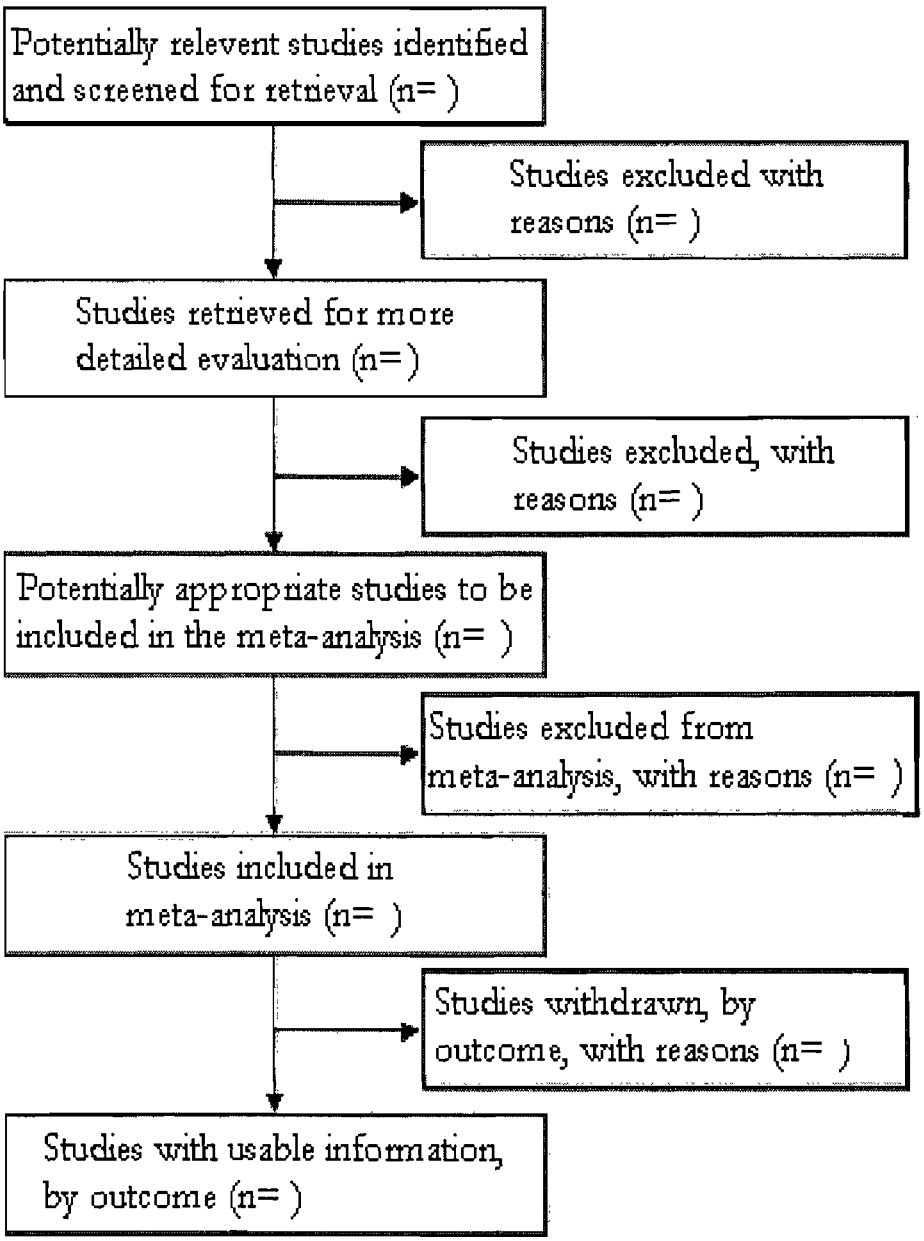
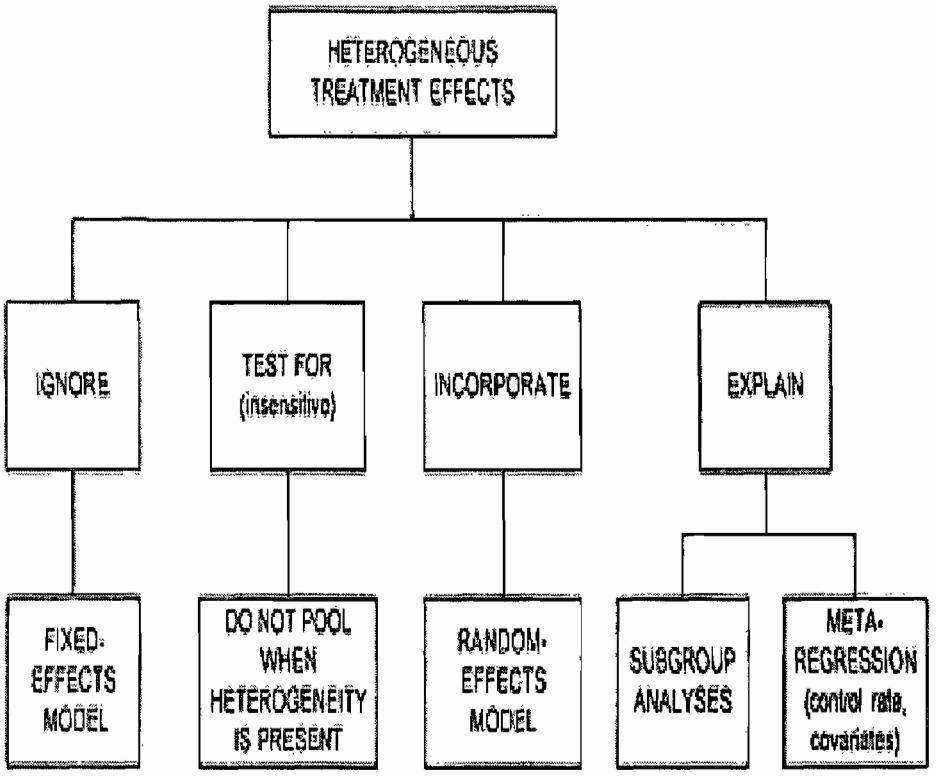


Tableau de prise de décision en cas d'hétérogénéité :

Table taken from Lau et al. (Lau, Ioannidis and Schmid 1997).



L'évaluation de la qualité des essais cliniques (a) :

Criteria taken from Jadad, et al. (Jadad, Moore et al. 1996).

Table 2	Items Considered by Individual Judges	
1.	Random allocation	(5)
2.	Blinding	(5)
3.	Clear/validated outcomes	(5)
4.	Description of withdrawals and dropouts	(5)
5.	Clear hypothesis and objectives	(4)
6.	Clear inclusion/exclusion criteria	(4)
7.	Power calculation	(4)
8.	Appropriate size	(3)
9.	Intention to treat	(3)
10.	Single observer	(3)
11.	Adequate follow-up	(3)
12.	Negative/positive controls	(3)
13.	Controlled interventions	(3)
14.	Appropriate analysis	(3)
15.	Randomization method explained	(2)
16.	Description of investigators and assessors	(2)
17.	Description of interventions	(2)
18.	Raw data available	(2)
19.	Compliance check	(2)
20.	Adverse effects documented clearly	(2)
21.	Comparable groups	(2)
22.	Clinical relevance	(1)
23.	Protocol is followed	(1)
24.	Informed consent	(1)
25.	Adequate analysis	(1)
26.	Appropriate outcome measures	(1)
27.	Data supporting conclusions	(1)
28.	Paper clear and simple to understand	(1)
29.	Ethical approval	(1)
30.	Appropriate study	(1)
31.	Independent study	(1)
32.	Overall impression	(1)
33.	Prospective study	(1)
34.	More than 1 assessment time	(1)
35.	Attempt to demonstrate dose response with new agents	(1)
36.	Appropriate duration of study	(1)
37.	Description of selection method	(1)
38.	Definition of method to record adverse effects	(1)
39.	Definition of methods for adverse effect management	(1)
40.	Objective outcome measurements	(1)
41.	Avoidance of data unrelated to the question addressed	(1)
42.	Representative sample	(1)
43.	Statistics, central tendency, and dispersion measures reported	(1)
44.	Blinding testing	(1)
45.	Results of randomization reported	(1)
46.	Analysis of impact of withdrawals	(1)
47.	Clear tables	(1)
48.	Clear figures	(1)
49.	Clear retrospective analysis	(1)

The number in parentheses indicates the number of judges who suggested each of the items.

L'évaluation de la qualité des essais cliniques- simplifié (b) :

Criteria is taken from Jadad (Jadad 1998).

1- Was the study described as randomized? (Add 1 point if yes)

2- Was the study described as double-blind? (Add 1 point if yes)

3- Was there a description of withdrawals and drop-outs? (Add 1 point if yes)

4- Was randomisation appropriate? (Add 1 point if yes, deduct 1 point if no)

5- Was the blinding appropriate? (Add 1 point if yes, deduct 1 point if no)

Tableau de l'évaluation de la qualité des études :

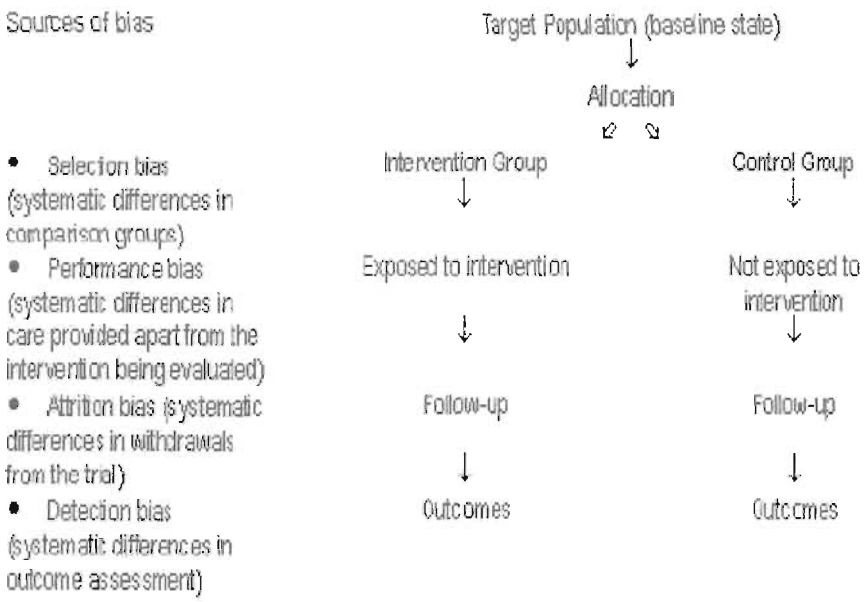
Table for quality assessment of the studies, developed by Cochrane (page 83) (Higgins and Green 2005)

Cochrane collaboration scale (code A, B, or C)

Risk of Bias	**Interpretation**	**Relationship of individual criteria**
A. Low risk of bias	Plausible bias unlikely to seriously alter the results	All of the criteria met
B. Moderate risk of Bias	Plausible bias that raises some doubt about the results	One or more criteria partly met
C. High risk of bias	Plausible bias that seriously weakens confidence in the results	One or more criteria not met

Tableau des sources de biais :

Table of the biased evaluation is developed by Cochrane (page 80) (Higgins and Green 2005).



Formulaire de codage :

Table is taken from Brown, et al (Brown, Upchurch et al. 1996).

TABLE 1: Selected Examples of Common Elements of a Study Coding Sheet: A Meta-Analysis of Strategies to Promote Weight Loss in Type 2 Diabetes

Study ID Number (1) _____
Author _____
Title _____
Journal _____
Year _____ Vol. _____ No. Pages _____

Methodological Features		
Publication date	_____	(2)
Source of reference	_____	(3)
Blinding of experimenter	_____	(4)
Assignment to groups	_____	(5)
Experimental mortality (%) from treatment group	_____	(6)
Experimental mortality (%) from comparison group	_____	(7)
Overall mortality rate (%)	_____	(8)
Research design	_____	(9)
Study Quality		
Study design	_____	(10)
Selection and specification of study sample	_____	(11)
Specification of illness or condition	_____	(12)
Description of weight loss intervention	_____	(13)
Definition of outcome construct	_____	(14)
Outcome measure	_____	(15)
Total quality points	_____	(16)
Substantive Features		
Professional affiliation of first author/experimenter	_____	(17)
Intervention Characteristics		
Type of intervention strategy	_____	(18)
Dietary strategy	_____	(19)
Contact frequency	_____	(20)
Length of each contact	_____	(21)
Total length of the intervention	_____	(22)
Dietary intervention approach	_____	(23)
Behavioral strategy	_____	(24)
Contact frequency	_____	(25)
Length of each contact	_____	(26)

L'Article

Amir Ali Sepehry, Stephane Potvin, Robert Elie, Emmanuel Stip. (2007). SSRI add-on therapy for the negative symptoms of schizophrenia: A meta-analysis. Journal of Clinical psychiatry, 68 (4): 604-610.

Selective Serotonin Reuptake Inhibitor (SSRI) Add-On Therapy for the Negative Symptoms of Schizophrenia: A Meta-Analysis

Amir Ali Sepehry, B.A.; Stéphane Potvin, Ph.D.; Robert Élie, M.D., Ph.D.; and Emmanuel Stip, M.D., C.S.P.Q.

Background: Negative symptoms are among the most chronic symptoms of schizophrenia. Even with the advent of atypical antipsychotic drugs, negative symptoms remain mostly refractory to treatment. It has been proposed that selective serotonin reuptake inhibitor (SSRI) augmentation therapy in schizophrenia could provide a greater relief of these symptoms. Published studies, however promising, have produced conflicting results.

Objective: To overcome this discrepancy in results, we performed a meta-analysis of studies assessing SSRI add-on therapy for the negative symptoms of schizophrenia.

Data Sources and Study Selection: A search was performed using the computerized search engines PsycINFO, PubMed (MEDLINE), and Current Contents. Keywords used were *schizophrenia* and (for SSRI) *sertraline*, *citalopram*, *paroxetine*, *fluoxetine*, and *fluvoxamine*. Hand search of published review articles as well as cross-referencing were carried out, too. Pharmaceutical companies were also contacted. Studies were retained if (1) SSRI add-on therapy was compared with antipsychotic monotherapy among schizophrenia-spectrum disorder patients; (2) the clinical trial was randomized, double-blind, placebo-controlled with parallel-arm design; (3) negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms or the Positive and Negative Syndrome Scale-negative subscale.

Data Extraction: With a consensus, authors (A.A.S. and S.P.) extracted and checked the data independently on the basis of predetermined exclusion and inclusion criteria. Effect size estimates were calculated using Comprehensive Meta-Analysis software.

Data Synthesis: Eleven studies responded to our inclusion criteria. Within a random-effects model, a nonsignificant composite effect size estimate for (end point) negative symptoms was obtained (N = 393; adjusted Hedges' g = 0.178; p = .191). However, when studies were divided according to severity of illness, a moderate and significant effect size emerged for the studies involving so-called "chronic patients" (N = 274; adjusted Hedges' g = 0.386; p = .014).

Conclusion: The current meta-analysis provides no global support for an improvement in negative symptoms with SSRI augmentation therapy in schizophrenia.

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Corresponding author and reprints: Emmanuel Stip, M.D., Centre de recherche Fernand-Seguin, 7331 Hochelaga, Montreal, Quebec, Canada H1N 3V2 (e-mail: emmanuel.stip@umontreal.ca).

Since Bleuler,[1] negative symptoms (apathy, avolition, anergia, alogia, blunted affect, and social withdrawal) of schizophrenia have been reported to be the core features of the disease. Particularly difficult to treat, these symptoms represent significant obstacles for reaching better global functioning.[2–4]

First-generation antipsychotic drugs (typical) provide only minimal relief of these enduring symptoms.[4] Second-generation antipsychotic drugs have been developed in the hope of eliminating the side effects of typical neuroleptics and of improving negative and cognitive symptoms. Even after such developments, negative symptoms remain mostly refractory to treatment.[5] Meta-analytic studies have reported benefits of second-generation antipsychotics in the treatment of negative symptoms, but these benefits appeared to be modest.[6,7]

A role for antidepressant drugs as adjuvant treatment of negative symptoms has been discussed by Silver.[8] The rationale for the use of antidepressant add-on therapy is based on the primary/secondary dichotomy. Negative symptoms are classified as primary or secondary.[9,10] In contrast with primary negative symptoms, which are directly related to the schizophrenia pathophysiology, secondary negative symptoms result from other psychiatric symptoms (e.g., positive symptoms), medication side effects (e.g., extrapyramidal symptoms), or medical conditions (e.g., mental retardation).[9,10] In particular, negative symptoms may be secondary to depressive symptoms, which share common key symptoms such as anhedonia, asociality, avolition, and apathy.[11,12] In this context, the use

of antidepressants has been thought to be of potential interest in schizophrenia, as the treatment of depressive symptoms would eventually lead to a relief of secondary negative symptoms. In clinical practice, it has been estimated that antidepressants are prescribed as adjunctive treatment in approximately one third of schizophrenia patients.[13] However, add-on therapy with antidepressants such as monoamine oxidase inhibitors (MAOIs)[14] or tricyclics[15] in schizophrenia has produced limited results.[16]

More recently, selective serotonin reuptake inhibitors (SSRIs) have been investigated as augmentation therapies for the negative symptoms of schizophrenia. On the basis of preliminary results, Silver[8] has proposed the usage of SSRI augmentation therapy for these enduring symptoms. However, other studies published so far have produced conflicting results.[17,18] A Cochrane registered systematic review by Whitehead et al.[19] showed that add-on antidepressant for persons with schizophrenia and comorbid depression may be of therapeutic value; yet, Whitehead et al. reviewed a small number of trials, which may have led to a possible study bias, so the interpretation of their result should be done with care. A new quantitative review of 7 trials (N = 202) by Rummel-and colleagues,[20] showed that combination of antipsychotics with antidepressants may perhaps be effective in controlling predominant negative symptoms. However, they report only 3 studies with SSRI (also included in our meta-analysis), and so to draw a conclusion on SSRI add-on therapy would be limited. Nevertheless, the authors assert that their finding needs to be substantiated by further larger-sized trials.[20]

Also it is noteworthy that the number of participants in these studies has been small, ranging from 20 patients[21] to 75 patients.[22] These studies did not include enough patients to detect a 20% difference between groups in symptom improvement, which is the clinical standard for the pharmacologic studies in schizophrenia.[23] To detect such a difference between groups, it is required that a trial include 131 participants per study arm ($\alpha = .05$; power, 80%).[24]

To reach the sample size required for detecting a 20% difference between groups (power, 80%), we conducted a meta-analysis of studies assessing SSRI add-on therapy for the negative symptoms of schizophrenia. This meta-analysis raised the sample size in each study arm to more than 131 participants. The results of this meta-analysis are of therapeutic importance, considering the chronic nature of negative symptoms. They could also shed light on the potential role of serotonin in the pathophysiology of negative symptoms.

METHOD

Data Sources

Systematic review of the literature on SSRI add-on therapy for the negative symptoms of schizophrenia was performed. Keywords used for the search were *schizophrenia* and (for SSRI) *sertraline*, *citalopram*, *paroxetine*, *fluoxetine*, and *fluvoxamine*. The search engines were PsycINFO, PubMed (MEDLINE) (1967–2005), and Current Contents (1993–2005). Hand search of published review articles, as well as cross-referencing, have been carried out to gather further data. When relevant, authors were contacted for missing data. Pharmaceutical companies were also contacted to retrieve unpublished data (no further records were found).

Study Selection

A consensus was reached among authors on the studies retained or discarded, on the basis of the following inclusion and exclusion criteria.

Inclusion Criteria

Studies were retained if (1) SSRI add-on therapy was compared with antipsychotic treatment; (2) patients had a diagnosis of a schizophrenia-spectrum disorder; (3) the clinical trial was randomized, double-blind, placebo-controlled with parallel-arm design; and (4) negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms (SANS)[25] or the Positive and Negative Syndrome Scale-negative subscale (PANSS-N),[26,27] before (baseline) and after follow-up (end point). Overall, these scales have been demonstrated to have high internal consistency and external validity for the population group.[27] Further, these scales have been reported to be relatively comparable.[15,28,31]

Exclusion Criteria

Studies were discarded if (1) schizophrenia patients had been diagnosed with comorbid obsessive-compulsive disorder (DSM criteria); (2) the study assessed the efficacy of MAOI, tricyclic, dual-action, or atypical antidepressants (e.g., bupropion); (3) the study had incomplete or unavailable data; or (4) a crossover study design was employed.

Data Extraction and Quantitative Data Synthesis

Two reviewers (A.A.S. and S.P.) independently extracted data; disagreements were resolved by consensus. Using Comprehensive Meta-Analysis,[32] effect size estimates were derived from the differences in negative symptoms between schizophrenia patients treated with add-on SSRI (SSRI group) and patients on placebo (placebo group), both before (baseline) and after treatment (end point). Effect size estimates were calculated from sample size, means, and standard deviations (PANSS-N score or SANS total score) for each group of patients: SSRI and placebo. When available, full data without attrition were preferred to intention-to-treat or last-observation-carried-forward data. Within a random-

Table 1. Study Characteristics of Randomized, Double-Blind, Placebo-Controlled Trials of SSRI Add-On Therapy for the Negative Symptoms of Schizophrenia

Study	N[a]	SSRI	SSRI Dosage (mg/d)	Antipsychotic	Scale	Patient Description	EPS/Depression Controlled	Treatment Duration, wk
Silver and Nassar[22]	30	Fluvoxamine	50–100	Unspecified	SANS	Chronic/Inpatient	Yes/Yes	5
Buchanan et al[21]	33	Fluoxetine	20–80	Clozapine	SANS	Nonresponder/Outpatient	No/Yes	8
Spina et al[38]	30	Fluoxetine	20	Typical	SANS	Chronic/Inpatient	**/Yes	12
Arango et al[35]	32	Fluoxetine	20	Typical	SANS	Outpatient	Yes/Yes	8
Silver et al[36]	52	Fluvoxamine	50–100	Typical	SANS	Chronic/Inpatient	Yes/Yes	6
Lee et al[17]	36	Sertraline	50	Typical	PANSS-N	Chronic/Inpatient	Yes/Yes	8
Poyurovsky et al[37]	24	Fluoxetine	20	Olanzapine	SANS	1st episode/Inpatient	No/Yes	8
Bustillo et al[18]	20	Fluoxetine	20–60	Olanzapine	PANSS-N	Outpatient	Yes/Yes	16
Salokangas et al[39b]	75	Citalopram	20–40	Typical	PANSS-N	Chronic/Outpatient	**/No	12
Mulholland et al[40]	20	Sertraline	50–100	Mixed	SANS	Chronic/Outpatient	**/Yes	4
Jockers-Scherubl et al[41]	25	Paroxetine	20–30	Mixed	PANSS-N	Chronic/Outpatient	**/Yes	12

[a]Number of patients who completed the trial.
[b]Data for this particular study were provided by the author.
Abbreviations: EPS = extrapyramidal symptoms, PANSS-N = Positive and Negative Syndrome Scale-negative subscale, SANS = Scale for the Assessment of Negative Symptoms, SSRI = selective serotonin reuptake inhibitor.
Symbol: ** = no data.

effects model, effect size estimates were derived using Hedges' g,[33] which provides effect sizes adjusted for sample size. Random-effects models, being more stringent than fixed-effects models, allow population-level inferences.[34]

In order to control for baseline clinical characteristics, effect size estimates were performed with available data (see Table 1). For age (7 studies), positive symptoms (10 studies), depressive symptoms (9 studies), and extrapyramidal symptoms (6 studies), effect estimates were calculated on the basis of mean scores and SDs for both comparison groups. In the case of sex (9 studies), the effect size estimate was computed as a nonparametric "rate difference," using male/female ratios. In addition, end point data were used to calculate effect size estimates for positive, depressive, and extrapyramidal symptoms. For some studies, extrapyramidal symptom total scores were not available, only extrapyramidal symptom subscale scores. These subscores were collapsed using D-STAT[32] to generate a total extrapyramidal symptom score (mean differences).

Homogeneity of Effect Size Estimates

It is more legitimate to aggregate effect size estimates when effect sizes are homogeneous. A universal mean to indicate the extent of heterogeneity (variability due to chance, due to scale used, etc.) is the application of statistical test, frequently portrayed as Cochran χ^2 test or the Q test/statistic. The Q statistic is similar to χ^2 statistics but uses meta-analytic data to examine the homogeneity of the effect sizes included in the studies.[43] Thus, we have calculated the Q statistic for the effect size estimates of the studies included in the meta-analysis (baseline and end point, separately). Significance was defined a priori as $p < .1$. A significant result is an indication of the presence of moderating variables within the dataset.

RESULTS

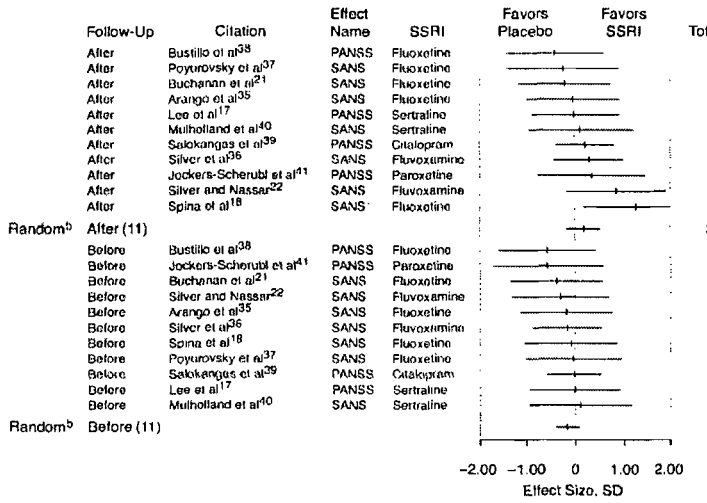
Study Characteristics

Five hundred ninety-one possible articles emerged. Of these, 552 studies were discarded on the basis of the evaluation of the abstract and 28 studies on the basis of the evaluation of the article, according to the following reasons: (1) type of article/study (e.g., review, case study, challenge study, survey, retrospective study, open-label trial, postmortem study, molecular study, letter to the editor, book chapter, and crossover study), (2) type of population (e.g., nonhuman subjects, patients with comorbid conditions, nonschizophrenia patients), (3) treatment type (e.g., non-SSRI antidepressants, nonpharmacologic therapy), and (4) incomplete or unavailable data.[34,46] The remaining 11 studies responded to our inclusion criteria (data were available for each study).

The 11 studies included in the meta-analysis were clinically heterogeneous (Table 1), in the following areas:

- SSRI medication: fluoxetine (5 studies), fluvoxamine (2 studies), sertraline (2 studies), citalopram (1 study), and paroxetine (1 study);
- antipsychotic drug: atypical (3 studies), typical (5 studies), not specified (1 study), and mixed (2 studies);
- psychiatric assessment: SANS (7 studies) and PANSS-N (4 studies);
- patient type (Note: Studies were classified according to population description explicitly stated by authors): chronic (7 studies) and nonchronic (4 studies);
- psychiatric setting: inpatient (5 studies) and outpatient (6 studies);
- treatment duration: from 4 weeks to 4 months;

Figure 1. Effect Sizes of Randomized Trials of SSRI Add-On Therapy for Negative Symptoms of Schizophrenia



	Follow-Up	Citation	Effect Name	SSRI	Total N[a]	Effect	p Value
	After	Bustillo et al[38]	PANSS	Fluoxetine	30	−.443	.223
	After	Poyurovsky et al[37]	SANS	Fluoxetine	24	−.282	.514
	After	Buchanan et al[21]	SANS	Fluoxetine	33	−.214	.534
	After	Arango et al[35]	SANS	Fluoxetine	32	−.053	.880
	After	Lee et al[17]	PANSS	Sertraline	36	−.016	.961
	After	Mulholland et al[40]	SANS	Sertraline	26	.103	.788
	After	Salokangas et al[39]	PANSS	Citalopram	75	.204	.376
	After	Silver et al[36]	SANS	Fluvoxamine	52	.280	.314
	After	Jockers-Scherubl et al[41]	PANSS	Paroxetine	25	.349	.380
	After	Silver and Nassar[22]	SANS	Fluvoxamine	30	.864	.022
	After	Spina et al[18]	SANS	Fluoxetine	30	1.278	.001
Random[b]	After (11)				393	.178	.191
	Before	Bustillo et al[38]	PANSS	Fluoxetine	30	−.606	.099
	Before	Jockers-Scherubl et al[41]	PANSS	Paroxetine	25	−.586	.147
	Before	Buchanan et al[21]	SANS	Fluoxetine	33	−.405	.244
	Before	Silver and Nassar[22]	SANS	Fluvoxamine	30	−.328	.364
	Before	Arango et al[35]	SANS	Fluoxetine	32	−.195	.575
	Before	Silver et al[36]	SANS	Fluvoxamine	53	.170	.537
	Before	Spina et al[18]	SANS	Fluoxetine	30	−.088	.806
	Before	Poyurovsky et al[37]	SANS	Fluoxetine	30	−.051	.888
	Before	Salokangas et al[39]	PANSS	Citalopram	67	−.023	.913
	Before	Lee et al[17]	PANSS	Sertraline	36	−.016	.962
	Before	Mulholland et al[40]	SANS	Sertraline	26	.101	.792
Random[b]	Before (11)				412	−.179	.072

[a]Ns in this figure pertain both to last-observation-carried-forward (LOCF) and intention-to-treat (ITT) data, as is the case for Bustillo et al. (LOCF) and Mulholland et al. (ITT).
[b]Analysis based on random-effects model.
Abbreviations: PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms, SSRI = selective serotonin reuptake inhibitor.

- type of data: last-observation-carried-forward or intention-to-treat (4 studies) versus study completers (7 studies).

It is noteworthy that 2 studies were not primarily designed to assess negative symptoms.[37,38] Studies reporting previously used data were withdrawn from analysis.[42–49]

Quantitative Data Synthesis

A total of 11 randomized, double-blind, placebo-controlled trials, with parallel-arm design (N = 393 patients at end point) were identified in which add-on SSRI therapy was compared with antipsychotic monotherapy. No significant differences were found between the treatment groups for negative symptoms using end point data (adjusted Hedges' g = 0.178; p = .191; random-effects model) (Note: An overall 5% attrition has been calculated.) (Figure 1). Interestingly, for baseline data, a composite effect size estimate for negative symptoms was obtained that bordered on significance (N = 412; adjusted Hedges' g = −0.179; p = .072), suggesting a potential study bias. For age, sex, and positive, depressive, and extrapyramidal symptoms, no significant differences between the SSRI and placebo groups were detected at baseline.

In order to control for masked effects, secondary analyses were performed. Effect size estimates for negative symptoms were calculated according to the following categories: antipsychotic type (typical, atypical, or mixed), SSRI medication (fluoxetine vs. others), psychiatric setting (inpatient/outpatient), psychiatric assessment (PANSS-N and SANS), and treatment duration (less than 12 weeks or longer than or equal to 12 weeks) (Note: In add-on SSRI for treatment of negative symptoms, a long-term duration of treatment of no less than 12 weeks is recommended[15]). These secondary analyses all provided nonsignificant composite effect size estimates for negative symptoms. A run was also performed excluding the studies by Bustillo and colleagues[38] and Poyurovsky et al.[37] A low and significant effect size estimate for negative symptoms was reached (N = 339; adjusted Hedges' g = 0.277; 95% CI = −0.087 to 0.640; p = .049). In addition, when studies were divided according to severity of illness (chronic/nonchronic), a moderate effect size for negative symptoms was obtained for the chronic group of studies (N = 274; adjusted Hedges' g = 0.386; 95% CI = −0.018 to 0.791; p = .014). Additionally, when studies were separated into last-observation-carried-forward or intention-to-treat versus study completers, similar results were yielded. Both effect estimates were nonsignificant and small: last-observation-carried-forward or

Table 2. Z Scores Obtained for Each Study

	Baseline		End Point	
Study	Placebo	Add-On SSRI	Placebo	Add-On SSRI
Buchanan et al[21]	-0.2465	0.1661	-0.0991	0.1219
Spina et al[18]	0.4650	0.5421	0.1908	-1.2916
Arango et al[35]	-0.1817	0.0260	0.0519	0.1038
Silver et al[36]	-0.0622	0.0895	0.1513	-0.1632
Silver and Nassar[22]	0.6276	1.0015	-0.4254	-1.2037
Poyurovsky et al[37]	0.7726	0.8178	-1.1366	-0.8255
Mulholland et al[40]	0.0880	-0.0176	0.0176	-0.0880
Salokangas et al[39]	0.3939	0.4166	-0.3676	-0.5802
Lee et al[17]	-0.0246	-0.0082	0.0082	0.0246
Bustillo et al[38]	-0.2367	0.3836	-0.3020	0.1551
Jockers-Scherubl et al[41]	0.3811	0.8675	-0.4104	-0.8302

Abbreviation: SSRI = selective serotonin reuptake inhibitor.

intention-to-treat (effect size = 0.093; p value = .594) and study completers (effect size = 0.240; p value = .225).

The set of 11 studies (end point data) included in the meta-analysis was slightly heterogeneous (Q = 16.830; p = .078). They were no longer heterogeneous when the studies were divided according to severity of illness (so called "chronic patients") (Q = 9.060; p = .170). Also, when the 2 studies not designed to primarily assess negative symptoms were excluded, effect size estimates of negative symptoms were no longer heterogeneous (Q = 12.312; p = .138).

Sensitivity Analysis

To control for the methodological shortcomings aforementioned (end point heterogeneity and baseline differences in negative symptoms), mean values reported by different researchers were transformed into z scores using their standard deviations for assessing a pooled variance (Table 2). The new data attained were then analyzed for differences between the 2 study conditions (SSRI vs. placebo) and between initial scores and final appraisal with a 2 × 2 factorial analysis of variance. The critical level of significance was set at 5%. Patients improved in time ($F = 21.94$, $df = 1,40$; $p < .001$) but no differences were observed between the 2 medication regimens ($F = 2.64$, $df = 1,40$; $p = .112$ NS). The same method was replicated for the so-called "chronic patients," and again time-treatment interaction emerged to be nonsignificant ($F = 0.88$; $df = 1,24$; $p = .357$).

DISCUSSION

The objective of this meta-analysis was to determine if SSRI add-on therapy provides relief of negative symptoms among schizophrenia patients. Using search engines, 11 randomized, double-blind, placebo-controlled trials were identified, involving 393 patients. Using Comprehensive Meta-Analysis,[32] effect size estimates for differences in negative symptoms (end point data) between both groups (SSRI and placebo) were calculated. Within a random-effects model, a nonsignificant composite effect size estimate was obtained, suggesting that SSRI augmentation therapy does not relieve the negative symptoms of schizophrenia. Secondary analyses were performed to control for potential confounding factors, such as psychiatric setting (inpatient/outpatient), psychiatric assessment (PANSS-N/SANS), antipsychotic type (typical/atypical/mixed), specific SSRI (fluoxetine vs. others), and treatment duration (shorter than 12 weeks or longer than or equal to 12 weeks). Again, no significant differences emerged between the SSRI and the placebo groups on negative symptoms. However, a significant but low effect size estimate for negative symptoms was obtained when the 2 studies not primarily designed to assess changes in negative symptoms (Bustillo et al.[38] and Puyurovsky et al.[37]) were excluded. In addition, a moderate and significant effect size for negative symptoms was reached using end point data when a run was performed with studies involving chronic patients. Of interest, these patients are the most likely to benefit from SSRI add-on therapy since negative symptoms are among the most enduring signs of the disorder.[2] Nevertheless, after a factorial analysis using baseline and end point data, even the so-called "chronic" schizophrenia patient did not seem to profit from this treatment regimen. Moreover, it must be taken into consideration that no operational definition of "chronic schizophrenia"—a stigmatizing term—has been consensually established.[50]

This first set of analyses comprised 2 limitations. First, a trend toward significance was observed when the composite effect size estimate was calculated for differences in baseline negative symptoms. Patients in the placebo group tended to have fewer negative symptoms at baseline, suggesting a potential study bias. In addition, end point effect size estimates for negative symptoms appeared to be heterogeneous. However, in the current meta-analysis, the heterogeneity problem must not be overestimated, for 2 reasons: (1) the number of studies included was small (11), which limits the power of the Q statistic,[51] and (2) for our secondary analyses (e.g., severity of illness), effect size estimates for negative symptoms were no longer heterogeneous.

To control for these shortcomings, means and SDs on PANSS-N and SANS scores were transformed into z scores (SSRI and placebo groups; baseline and end point data), allowing for the calculation of a composite 2 × 2 factorial analysis of variance of negative symptoms, with group and time as independent variables. A nonsignificant result was obtained, further suggesting that SSRI augmentation therapy does not relieve the negative symptoms of schizophrenia.

The results of the current meta-analysis provide no clear evidence for the presumed efficacy of SSRI augmentation treatment of negative symptoms. Whereas previous studies

relied on samples too small to detect clinically significant differences, pooling of the published randomized, double-blind, placebo-controlled studies that were methodologically homogeneous provided a sample of more than 150 patients per arm; however, the global sample size for the 11 studies remained small (393 patients). In addition, the study provides evidence that this lack of efficacy can not be attributed to clinical differences in age, sex, positive symptoms, depressive symptoms, or extrapyramidal symptoms. However it is imperative to touch base with clinical and methodological issues in this debate. For discussion of clinical implications and methodological concerns related to primary and secondary negative symptoms, please refer to the studies by Moller[52] and Rummel and colleagues.[20]

In conclusion, our findings offer no support for polypharmacy—combining antipsychotics and SSRI—at least not for the treatment of negative symptoms of schizophrenia for which there was a poor response to antipsychotics alone.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), clozapine (Clozaril, FazaClo, and others), fluoxetine (Prozac and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft).

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Résumé de l'article (en français)

Parmi les signes qui font partie de la définition clinique de la schizophrénie, figurent les symptômes négatifs. Ces symptômes négatifs (le retrait social, l'émoussement des affects, l'avolition, etc.) sont des signes qui sont difficiles à traiter. Même avec l'arrivée des antipsychotiques atypiques, les symptômes négatifs demeurent la plupart du temps réfractaires au traitement. Alors, une hypothèse a été proposée, l'examen de l'effet de la potentialisation des médicaments antipsychotiques par les ISRS pour traiter les symptômes négatifs. Les résultats d'essais contrôlés, de quelque manière prometteuse, ont produit des résultats contradictoires. **Objectifs** : Pour surmonter cette anomalie dans les résultats, nous avons examiné l'effet de la potentialisation des médicaments antipsychotiques par les ISRS pour traiter les symptômes négatifs en utilisant une approche de revue de littérature quantitative. **Méthode** : Une recherche a été exécutée en utilisant les moteurs de recherche automatisés, le PsychINFO, le PubMed (Medline), et le Current Contents. La recherche manuelle des articles de type de synthèse aussi bien que par vérification des références d'article publié ont été effectuées. Des compagnies pharmaceutiques ont été également contactées. Des études ont été maintenues si : (i) La poly-pharmacie avec ISRS a été comparée au monotherapy antipsychotique avec des patients schizophrène ; (ii) l'essai clinique formé de façon randomisée, à double aveugle, et parallèlement contrôlé par la voie de placebo; (iii) des symptômes négatifs ont été évalués avec le « SANS » ou avec le sous échelle de « PANSS » pour les symptômes négatif. Avec un consensus, AAS et SP ont extrait et vérifié les données indépendamment basées sur des critères d'exclusion et

d'inclusion prédéterminée. Des évaluations de la taille de l'effet ont été calculées en utilisant le logiciel « Comprehensive Meta-Analysis ». **Résultats** : Onze études ont répondu à nos critères d'inclusion. Avec un modèle d'effet d'aléatoire « random effect model », une taille de l'effet non-significative (sur la fin des études) pour des symptômes négatifs a été obtenue (N= 393; Hedges' g= 0.178; p= 0.191). Cependant, quand des études ont été divisées selon la sévérité de la maladie, une taille de l'effet modérée et significative a émergé pour les études faisant participer des patients prétendus 'chroniques' (N= 274; Hedges' g= 0.386; p= 0.014). **Conclusion** : La méta-analyse que nous avons effectuée montre un effet négligeable pour amélioration des symptômes négatifs en poly-thérapie avec ISRS dans la schizophrénie.

Permission des co-auteurs

L'Échelle D'appréciation des Symptômes Négatifs (SANS) :

SANS scale takend from Lecrubier and Boyer (Lecrubier and Boyer 1987; Lecrubier 1997).

ÉCHELLE D'APPRÉCIATION DES SYMPTÔMES NÉGATIFS (DÉFICITAIRES)

(SCALE FOR THE ASSESSMENT OF NEGATIVE SYMPTOMS)

SANS

N.C. ANDREASEN
FEUILLE RÉSUMÉE DE COTATION*
Traduction française : Y. LECRUBIER et P. BOYER

NOM ☐☐☐☐☐☐☐☐☐☐☐☐☐☐ PRÉNOM ☐☐☐☐☐☐☐☐☐☐☐☐☐☐

SEXE ☐ AGE ☐☐ DATE ☐☐☐☐☐☐

EXAMINATEUR ☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Reporter l'intensité selon le système général suivant :

0 - absente - aucun(e) - inexistant.
1 - doute (sur une diminution) - discutable.
2 - léger(e)
3 - moyenne(e).
4 - important(e).
5 - sévère - grave.

RETRAIT OU PAUVRETÉ AFFECTIVE

1 - Expression figée du visage ☐

L'expression faciale apparaît rigide, figée, mécanique. On note une absence, ou une diminution, des changements d'expression en rapport avec le contenu du discours.

2 - Diminution des mouvements spontanés ☐

Le patient est assis, immobile durant l'entretien, et présente peu, ou pas, de mouvements spontanés. Il ne change pas de position, ne bouge pas ses membres...

3 - Pauvreté de l'expression gestuelle ☐

Le malade n'utilise pas les mouvements de son corps pour aider à l'expression de ses idées, tels que gestes des mains, posture penchée en avant...

4 - Pauvreté du contact visuel ☐

Le malade évite de regarder l'autre ou d'utiliser ses yeux pour s'exprimer. Son regard semble perdu dans le vide, même lorsqu'il parle.

5 - Absence de réponses affectives ☐

Ne rit ou ne sourit pas lorsqu'il y est incité.

6 - Affect inapproprié ☐

L'affect exprimé est inapproprié ou incongru et non simplement pauvre et émoussé.

7 - Monotonie de la voix ☐

Lorsqu'il parle, le malade ne présente pas les modulations vocales normales. Le discours est monotone.

8 - Évaluation globale de la pauvreté affective ☐

L'évaluation globale prend en compte la gravité de l'ensemble de l'émoussement affectif. Une importance particulière doit être donnée au noyau représenté par l'absence de réactivité, une diminution globale du vécu émotionnel, et son caractère inapproprié.

sous-score : somme 1 à 7 ☐☐

ALOGIE

9 - Pauvreté du discours ☐

C'est la réduction de la quantité de propos spontanés, aboutissant à des réponses brèves, concrètes et non élaborées aux questions.

10 - Pauvreté du contenu du discours (idéique) ☐

Bien que les réponses soient suffisamment longues pour que le discours soit normal en quantité, il comporte peu d'informations. Le langage tend à être vague, souvent trop abstrait ou concret, répétitif, stéréotypé.

11 - Barrages ☐

Le malade décrit spontanément, ou à partir d'une question, une interruption du cours de sa pensée

12 - Augmentation de la latence des réponses ☐

La durée qui s'écoule avant que le malade ne réponde aux questions est plus longue que normalement. Il peut sembler "ailleurs". Il a cependant compris la question

13 - Évaluation globale ☐

Les signes nucléaires de l'alogie étant la pauvreté du discours et celle de son contenu, l'évaluation globale doit particulièrement en tenir compte.

sous-score : somme 9 à 12 ☐☐

AVOLITION - APATHIE

14 - Toilette - hygiène ☐

Vêtements négligés ou sales, cheveux graisseux, odeur corporelle...

15 - Manque d'assiduité au travail ou à l'école ☐

Le malade a des difficultés à trouver ou garder un emploi, ou une insertion scolaire en rapport avec son âge, à effectuer les travaux ménagers. S'il est hospitalisé, il ne participe pas de façon durable aux activités du service.

16 - Anergie physique ☐

L'inertie est physique : le sujet peut rester des heures assis sur une chaise, sans entreprendre spontanément une activité.

17 - Évaluation globale ☐

Un poids important peut être accordé à un ou deux symptômes prédominants dans l'évaluation globale s'ils sont particulièrement frappants.

sous-score : somme 14 à 16 ☐☐

ANHEDONIE - RETRAIT SOCIAL

18 - Intérêts et activités de loisirs ☐

Le malade présente peu de centres d'intérêts, peu d'activités ou de "hobbies". L'évaluation doit prendre en compte les aspects qualitatifs et quantitatifs de ces intérêts

19 - Intérêts et activités sexuels ☐

Les malades peuvent présenter une diminution des intérêts et activités sexuels ou du plaisir correspondant

20 - Incapacité à vivre des relations étroites ou intimes ☐

Le malade peut présenter une incapacité à développer des relations étroites ou intimes, en particulier avec sa famille ou des sujets du sexe opposé

21 - Relations avec les amis et collègues ☐

Le malade peut avoir peu, ou pas d'amis et faire peu d'efforts pour y remédier, choisissant d'être pratiquement tout le temps seul.

22 - Évaluation globale de l'anhédonie et du retrait social ☐

L'évaluation globale doit rendre compte de la sévérité de l'ensemble symptomatique anhédonie-retrait social en tenant compte des normes attendues selon l'âge, le sexe, le statut familial

sous-score : somme 18 à 21 ☐☐

ATTENTION

23 - Inattention dans les activités sociales ☐

Au cours de ses activités, ou relations sociales, le malade paraît inattentif. Il semble "perdu"

24 - Inattention durant la cotation ☐

Pour l'évaluer on peut demander d'épeler le mot "MONDE" à l'envers ou proposer des épreuves arithmétiques simples tenant compte du niveau scolaire. Score 0 = 0 erreur, Score 1 = 0 erreur, mais il/elle hésite, Score 2 = 1 erreur, Score 3 = 2 erreurs, Score 4 = 3 erreurs, Score 5 = plus de 3 erreurs.

25 - Évaluation globale ☐

L'évaluation globale des possibilités d'attention ou de concentration, doit tenir compte des éléments cliniques et des performances aux tests.

sous-score : somme 23 à 24 ☐☐

score total (somme de tous les items) ☐☐☐

somme des sous-scores ☐☐

somme des évaluations globales ☐☐