FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2011/2012

Sara Sofia Amaral Carneiro

Late-Onset Schizophrenia: a Systematic Review

março, 2012

FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

Sara Sofia Amaral Carneiro

Late-Onset Schizophrenia: a Systematic Review

Mestrado Integrado em Medicina

Área: Psiquiatria e Saúde Mental

Trabalho efetuado sob a Orientação de:
Doutor Rui Manuel Bento de Almeida Coelho

Trabalho organizado de acordo com as normas da revista:
BioMed Central Psychiatry

março, 2012

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR
PROJETO DE OPÇÃO
DISSERTAÇÃO / MONOGRAFIA

Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

Eu, Sara Sofia Amaral Carneiro, abaixo assinado, nº mecanográfico 060801249, estudante do 6º ano do Mestrado Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 20/03/2012

Assinatura: Sara Sofia Amaral Carneiro

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR PROJETO DE OPÇÃO DISSERTAÇÃO / MONOGRAFIA

Projeto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

Nome: Sara Sofia Amaral Carneiro

Endereço eletrónico: med06249@med.up.pt **Telefone ou Telemóvel**: 964860801

Número do Bilhete de Identidade: 13459114

Título da Monografia:

Late-Onset Schizophrenia: a Systematic Review

Orientador:

Doutor Rui Manuel Bento de Almeida Coelho

Ano de conclusão: 2012

Designação da área do projeto:

Psiquiatria e Saúde Mental

Faculdade de Medicina da Universidade do Porto, 20/03/2012

Assinatura: Sara Sofia Amaral Carneiro

Late-Onset Schizophrenia: a Systematic Review

Sara SA Carneiro[1]

[1]Departamento de Neurociências Clínicas e Saúde Mental – Unidade Psiquiatria, Faculdade de Medicina da Universidade do Porto, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal.

Email addresses:

SSAC: med06249@med.up.pt

carneiro.sara@gmail.com

Abstract

Background

Schizophrenia usually onsets from late adolescence to the third decade of life (Early-Onset Schizophrenia), although it may onset during childhood or later in adult life (15%-23,5% >40 years and 3%-4% >60 years). Late-Onset Schizophrenia (LOS) is the term applied to the rare cases of Schizophrenia whose diagnosis is made after 40 years of age.

Given the lack of studies gathering the multiple areas of data about LOS, we found pertinent to review this theme. The main goal of this article is, then, to review knowledge available for LOS, namely its clinics, risk factors, delaying factors for Schizophrenia (including recent findings at the molecular level), prognosis and its association with organic central nervous system disease. This will be done emphasizing similarities and disparities relative to EOS which may contribute to the central debate about etiopathogenic differences/resemblances between both patient groups.

Methods

A database search on PubMed Articles published between 1 January 2005 and 31 December 2011 was undertaken, based on research keywords: "late-onset schizophrenia", "late onset schizophrenia", "late-onset psychosis" and "paraphrenia". In addition, we screened related studies and reference lists of identified studies. We included studies published in English and French.

Results

The systematic search yielded a total of 241 unique studies. After the screening of titles and abstracts, the full article assessment and the adding of relevant references, a total of 50 studies revealed to be of interest and provided the base for the present systematic review.

Conclusions

Great difficulties remain inherent in the study of LOS, arising from lack of works in this population and from discrepancies among them in what concerns study designs and methods of analysis.

There are well-established differences in clinical features between LOS and EOS patients, attributing clinical utility to this subdivision of Schizophrenia.

It has been described a molecular factor specifically associated with LOS and not with Schizophrenia in general – CCR5 32bp deletion allele.

Subdivision of Schizophrenia proposed by the International Consensus remains unclear about its pathophysiologic validity, as current evidence points to the possibility of LOS representing a heterogeneous group of patients, including delayed forms of EOS and distinct pathogenic entities.

Keywords: Schizophrenia; Late-Onset Schizophrenia; Early-Onset Schizophrenia; CCR5; NPY; dementia;

Background

Schizophrenia is a clinical syndrome characterized by a profoundly disruptive psychopathology that involves cognition, emotion, perception, and other aspects of behavior. It affects roughly 1% of world population and it usually onsets from late adolescence to the third decade (Early-Onset Schizophrenia - EOS), although in a significant portion of cases symptoms begin during childhood (4% <18 years) or later in adult life (15%-23,5% >40 years and 3%-4% >60 years), and even at 100 years of age. [1-3].

Manfred Bleuler, in 1943, studying the particularities of patients whose symptoms developed later in life, was the first to suggest a clinical subdivision of Schizophrenia by age of onset [4]. However, this subdivision was neither widely adopted nor criteria-consistent in the scientific community, including between International Classification of Diseases (ICD) and Diagnostic and Statistical Manual of Mental Disorders (DSM) [5-7]. Only in 2000 the "International Consensus" postulated diagnostic distinction of later-onset cases by reviewing the rationale about their validity and clinical utility. This document, elaborated following the gathering and agreement of experts in the matter constituted an evidence-based attempt to overcome the discordance in this subject and to stimulate research about the specificities of these groups of patients. It classified cases of later onset of Schizophrenia symptomatology either as Late-Onset Schizophrenia (LOS) and Very-Late-Onset Schizophrenia-Like Psychosis (VLOSP). Late-Onset Schizophrenia (LOS), the subject of this work, was then defined as cases in which Schizophrenia criteria are met after the 40 years of age but before 60 years of age (the cut-off age for VLOSP).

Underlying the study of the clinical and epidemiologic particularities of LOS is also the question of its etiopathogeny. In the case of EOS, from which much more

studies are available, the question of etiopathogeny remains largely unknown, despite being generally accepted to be due to a neurodevelopment defect [8]. Hence, if we aim to understand etiology and pathological mechanisms leading to LOS, the first big problem concerns the extent to which its underlying mechanisms are different from EOS. From this point of view, several questions may be raised, which may not be mutually exclusive: is LOS a delayed form of EOS or does it constitute a distinct mechanistic entity? If the pathologic processes are the same, what explains the later onset of the disorder? If the pathologic processes are not the same, in which degree is the etiopathogeny different from the typical Schizophrenia cases? Is there a pathological role played by Central Nervous System (CNS) aging in the development of LOS? Is there any contributing role played by neurodegenerative and cerebrovascular diseases? Is there any kind of role for gender? Can the answer be a combination of some of the previous hypothesis? There are different possible approaches that may give clues to the questions above, and they range from the molecular to the clinical level

We found the theme of LOS important to review given (1) the lack of recent works gathering latest knowledge about its clinics, epidemiologic and biologic specificities; (2) also because of the interesting debate that its etiopathophysiology permits, since it is a group of patients whose age is situated between the non-organic EOS group and the recognized organic forms constituting VLOSP.

So, the main goal of this article is to review the data available for LOS, namely its clinics, risk factors, delaying factors of Schizophrenia, prognosis and possible associations with organic central nervous system disease. This will be done emphasizing similarities and disparities of the same data relative to the EOS-group, in order to discuss the questions mentioned above, related to possible ethiopathogenic

similarities and differences between LOS and EOS. Also, inherent in research on the topic there are numerous difficulties which will be addressed initially in the article.

Methods

Literature search

A database search on PubMed Articles published between 1 January 2005 and 31 December 2011 was undertaken, based on research keywords: “late-onset schizophrenia”, “late onset schizophrenia”, “late-onset psychosis” and “paraphrenia”. The literature search yielded the identification of 371 possibly eligible articles.

Eligibility assessment

A stepwise approach was used in the selection process. First, each title and abstract were screened in accordance with the following inclusion criteria that were developed a priori: (1) Study participants must have a medical diagnosis of Schizophrenia, LOS, VLOSP or Paraphrenia; (2) Studies must be written in English, French, or Portuguese. Second, studies were excluded if they focused only in characteristics within Early-Onset Schizophrenia cases. Third, full articles were also read if a title and its abstract did not provide sufficient information for exclusion. Finally, relevant references were considered.

Results

The systematic search yielded a total of 241 unique studies. After screening of titles and abstracts, 39 were considered potentially relevant. After the full article assessment, 35 articles were retrieved. Also, 15 relevant references were added. A total of 50 studies revealed to be of interest and provided the base for the present systematic review (Figure 1).

Discussion

LOS research difficulties and the International Consensus

A considerable amount of obstacles are inherent to LOS research, some of them expectable given the previously mentioned discrepancies in the scientific community in the "pre-Consensus era" in what concerns to the subject. These difficulties may be schematized as: (1) discrepancy in the terminology and criteria used to define LOS patients, (2) poor research using this specific population and, finally, (3) lack of uniformity on the methods used in the assessment of patients and data analysis [9-12]. The general consequences that arise are of two types: significantly increased difficulty in the process of bibliographic review and need for meticulous care when trying to extrapolate data for LOS from studies that include patients whose symptoms begin later in life.

Terminology used to classify patients whose symptoms begin later in adult life show lack of homogeneity since Bleuler . Among the different studies, cases with criteria for LOS have been called: "Late-Onset Schizophrenia", "Late Paraphrenia" or a larger group "Late-Onset Psychosis". [2, 5, 9, 10].

The term paraphrenia refers to a condition characterized by a strong delusional component with preservation of thought and personality**,** with a chronic course leading to a significant degree of cognitive impairment [13]. Furthermore, some works use the term "late paraphrenia" to refer onset after 60 or 65 years old, while others use it to differentiate from older chronic Schizophrenia patients or to emphasize the many distinguishing features that set apart late-life psychosis from Schizophrenia [13].

Late-Onset Psychosis is characterized by a well-organized delusional system, with or without hallucinations and with no obvious deterioration in personality or intellect, with onset after 40 years old or after 60 years old [14, 15].

In what concerns LOS criteria, the rare research work that analyses data specifically for a group of age of onset (and not Schizophrenia cases as a whole) do not always obey to a uniform cut-off to define LOS. The cut-off age to define LOS (found in the literature) range from 40 to 65 years of age [15-19]. Adding to this, the number and sample sizes of LOS studies compared with those regarding EOS or childhood Schizophrenia is scarce [12].

Our review also found several different criteria among studies to establish this age of onset: first psychotic symptoms [5, 9, 15, 17, 20], first contact with psychotic service [21, 22], first manifestation of prodromal symptoms [10]. This difficulty may be increased in LOS cases due to their less severe symptomatology, which make the recognition of the initial symptoms more difficult [10, 12, 23-27].

Yet another difficulty relates to the tests used to measure features and the type of statistical analysis involved, which may lead to different results [10, 12, 15]. Also, some divergent findings could possibly be attributed to the heterogeneity of the studies' samples, which not only included patients with Schizophrenia diagnosed by ICD or DSM criteria, but they also included other psychiatry disorders [15].

The International Consensus

Taking all these difficulties into account, and in order to stimulate more research to better understand the pathophysiology and etiology of schizophrenias, the International Late-Onset Schizophrenia Group, in the year 2000, reviewed and discussed the evidence about this matter and suggested the recognition of two classes of late-onset psychotic disorders based on the age at onset of first psychotic symptoms: a Late-Onset Schizophrenia (LOS: onset > 40 years), and a Very-Late-Onset Schizophrenia-Like Psychosis (VLOSP: onset > 60 years) [5]. VLOSP replaced both terms "Late Paraphrenia" and "Paraphrenia", and it also includes: Schizophrenia, Delusional Disorders, Schizoaffective Disorder, Bipolar Disorder with Psychotic Features, Paranoid Psychosis and Psychosis "Not Otherwise Specified", with age of onset after 60 years old [5, 13, 28]. Studies measuring the impact of this document in the concordance of diagnostic stratification of Schizophrenia, nomenclature and cut-offs used are missing.

Currently, in ICD-10 (year 1993) and DSM-IV-TR (year 2000) the LOS group of patients fall into the category "Schizophrenia", although DSM-IV-TR refers to the cases of Schizophrenia with onset after 45 years of age as having some different characteristics from the group of patients whose disorder begins early in life [6, 7].

This review article considered LOS as the designation attributed to the group of schizophrenic patients whose symptoms begin later than 40 years of age.

LOS Clinical features:

Symptomatology, response to treatment and prognosis

LOS Symptomatology

Diagnostic criteria for LOS corresponds to a set of symptoms similar to those in EOS [5]. This fact and the efficacy verified to the same class of drugs (which will be discussed later) remain the strongest rational base to hypothesize a mechanistic homogeneity between LOS and EOS. DSM-IV-TR and ICD-10 diagnostic criteria for Schizophrenia are summarized in tables 1 and 2, respectively.

Despite obeying to the same diagnostic criteria than EOS, LOS patients show some well-established clinical differences in comparison to patients with EOS (summarized in table 3). LOS is more often in the female gender [5, 13, 15, 17, 20]; it is more likely than EOS to have multimodal hallucinations, systematized delusions, persecutory delusions and a better premorbid function [5]; it has less family history of Schizophrenia [5, 13, 15]; it is less likely to have thought disorders (specially formal thought disorders), affective bluntness, disorganization conducts, severe positive symptoms [5, 15].

Knowledge is still sparse and controversial regarding the LOS cognitive performance, with some studies finding no differences between LOS and EOS while others found differences in both directions [15]. In order to determine if the chronicity effect and extensive use of typical neuroleptics could influence cognitive deficits, a meta-analyses compared in-treatment LOS patients with first-episode EOS patients [12]. That study found that those LOS patients have more cognitive impairment than first-episode EOS ones. So, the findings concerning differences in cognitive performance in LOS versus EOS seem to be susceptible to disparities in time-course of

disease and treatment between both patient samples. There are no studies available, however, that compare first-episode LOS patients with first-episode EOS patients, neither studies that adjust for age and time-course of outpatients. Nevertheless, regarding the cognitive profile, LOS seems to have a specific rather than generalized cognitive deficits, not explainable only by aging and related factors, which points to disturbed circuits being specific rather than generalized in LOS [12].

Worthy of emphasis is that most of the differences between EOS and LOS that we have been discussing remained significant even after adjustments in age, gender, severity of negative symptoms, and duration of illness [5]. Also, the hypothesis that Deficit Syndrome, a variant of Schizophrenia disorder characterized by enduring, idiopathic negative symptoms and more severe course of illness, is over-represented in EOS has been ruled out, showing that it does not contribute to the LOS-EOS' clinical differences [5, 10].

LOS response to treatment

It is expected that an equally good response from LOS patients to the same treatment used in EOS patients represents the targeting of common pathogenic mechanism(s). Additionally, it is not surprising that LOS-patients have been receiving similar therapies (both pharmacologic and non-pharmacologic) as this subgroup was only recently formally recognized. This led to the observation that the same antipsychotic therapy exhibits the similar efficacy between LOS and EOS. Antipsychotics are, therefore, a mainstay of LOS therapy [5]. Nonpharmacological treatment (including psychological management, social skills training, cognitive-behavioral treatment) has shown to be a helpful adjunct to pharmacotherapy as in EOS

cases [5, 29]. Repetitive transcranial magnetic stimulation efficiently reduces resistant auditory hallucinations, both in acute and maintenance treatment, also as in EOS cases [30].

An important and well established characteristic of LOS patients is that a less dosage of neuroleptics ($^1/_4$ to ½) is needed to achieve a same symptomatic improvement when comparing to EOS cases [5, 15]. Comparing old age schizophrenic in-treatment patients (LOS and chronic EOS patients) with healthy controls, it was verified that the formers were not achieving a normal state of functioning, but rather were returning to a premorbid state of suboptimal and somewhat impaired function [31].

Drug treatment should be started at very low doses and increases in dosages should be made slowly [2, 5]. Use of depot medication at very low doses may be successful in ensuring compliance [5]. With the exception of clozapine, the atypical antipsychotic agents are clearly advantageous, because of the reduced likelihood of extrapyramidal symptoms and tardive dyskinesia for which elderly patients are at higher risk [5, 31]. However, even atypical antipsychotic agents have important side effects, in particular on cardiovascular and metabolic function, diabetes, and lipid levels [31]. This is an important finding because the most common cause of death among schizophrenics is heart disease (like in the general population), yet it has been estimated that persons with Schizophrenia on average die 10 years earlier than the general population [32, 33].

Despite patients with Schizophrenia do not achieve same symptomatic remission with atypical agents than with typical ones, the use of the former is justifiable by the reduction of the typical antipsychotic drugs side effects, leading expectedly to a better global health in older schizophrenic patients [5]. At this point, it is relevant to refer that there is a great variety of criteria to define remission, which compromises solid conclusions [31]. Therefore, regarding the differences in dosage of antipsychotic drug

treatment, it is conceivable that it could be partially attributable to (1) a tendency to continue prescribing higher doses to EOS patients (who received their first antipsychotic prescription in an era when average dose recommendations were higher for first-break psychosis); (2) reflection of the EOS residual / anchoring effects (clinicians being hesitant to change medication doses for clinically stable patients); (3) secondary factors, such as episodes of hostility or aggression being less prevalent among LOS compared to EOS patients; or (4) an increasing pharmaco-sensitivity due to less chronic symptomatology [10, 28]. Nevertheless, answer(s) to these hypotheses are still not possible from the data available.

A new, potentially safer and interesting antipsychotic treatment based on estrogen (whose rationale will be discussed later) has been tested in schizophrenic patients. However, the results from a clinical trial in which estradiol is administered in schizophrenic EOS women are not consistent [34-36]. Moreover there is still considerable research to be done to determine the correct dose and duration of use of estradiol, its safe use in women and men with Schizophrenia (EOS) with respect to the known side effects, and whether it may be used eventually as a stand-alone medication rather than as an adjunct [37]. A case reporting estrogen replacement therapy alone in a periclimacteric patient with LOS experiencing severe symptoms attained remission [38]. A case reporting phytoestrogen (chemical structure similar to estradiol) revealed improvement in depressive symptoms of a LOS patient, as adjuvant to atypical antipsychotic treatment [39].

LOS Prognosis

When we talk about prognosis in the context of Schizophrenia we refer both to symptom remission after treatment and also to the chronic course of the disease, assessing neurocognitive evolution, i.e. whether dementia develops or not.

The question of symptom remission in LOS has been treated previously in this paper.

In what concerns to cognitive course, cross sectional studies have not found accelerated cognitive decline in the lifespan of patients with LOS when compared with healthy controls.

Other studies compared chronically hospitalized Schizophrenia cases with outpatients. Particularly, one study that compared chronically hospitalized LOS patients with EOS patients and, observed that during their clinical evolution, the first patients were more likely to suffer cognitive deficits (frequently of executive functions and thought disorder) than EOS patients [40]. On the other hand, in what concerns the course of cognitive performance in chronically hospitalized EOS patients when comparing to LOS cases, some studies have shown that there is a decrease in the test performance of permanently hospitalized patients with chronic Schizophrenia as age and illness duration increased; contrarily, LOS patients showed no significant cognitive decline after several years of follow-up [41]. This study also adjusts for age and years of evolution. This better prognosis found by some works makes it questionable whether the results would be the same after adjustment for the effect of ageism, the tendency to underdiagnose and undertreat older people [5, 31, 42]. Together with the previous data, this may suggest that Schizophrenia prognosis depends more on the severity of its clinical features (and, hence, to the activity of the pathologic processes) and not in the age context (CNS maturity and aging) in which the disorder onsets. In other words, the

age of onset seems not to shape clinical phenotype of Schizophrenia (at least in the long term). Ignoring some expectable non-adjustable differences between chronically institutionalized patients and outpatients with Schizophrenia, these previous findings may suggest that EOS and LOS-associated mechanisms have a chronic deleterious impact in the functionality and/or integrity of pathways involved in cognition, at least in severe forms. Curiously, a recent prospective study analyzed the issue of cognitive decline in later age of onset of Schizophrenia with a strong sample of near 8000 cases of LOS and VLOSP patients [22]. With a follow-up of 3 to 4 ½ years, they found two to three times more risk of dementia in LOS patients when comparing to age-matched osteoarthritis patients. If this association is due to course of disease, association with other neurodegenerative diseases or with protection from osteoarthritis patients is not yet possible to tell. On the other side, exhaustive neuropsychological data to evaluate dementia in the initial diagnosis of Schizophrenia is not postulated and was not done in this study.

The impact of Schizophrenia (at least in its severe forms) found by some studies seems not to be due to an accelerated process of aging since most neuroimaging abnormalities associated with aging are not shared with LOS subgroup, with the exception of thalamic enlargement, a feature not observed in EOS patients (table 4). Hence, either pathologic processes underlying LOS are different from EOS (namely those affecting cognitive pathways) and accelerate some features associated with CNS aging (i.e. thalamic enlargement) or Schizophrenia in general has its own ways to deteriorate cognitive function, at least in their severe forms, and those are independent of ageing.

Nevertheless, more studies in the matter are needed as currently it seems not possible to have a solid amount of data to address the question of neurocognitive evolution in LOS, and comparative to EOS.

Given the general observations of less severe symptomatology, less doses required to achieve same clinical response and that severity-adjusted groups of EOS and LOS experience similar cognitive decline, the following questions about etiopathogeny of LOS relative to that of EOS become pertinent: can these differences be derived to LOS constituting a delayed and more attenuated form of the same perturbed mechanisms? Or is LOS a form of Schizophrenia associated with its own pathogenic mechanisms that dictate these clinical differences relative to EOS?

Some data indicate that differences in symptom profiles with onset across the age span could represent: (1) cohort difference; (2) age-associated central nervous system differences independent of the illness; (3) differences in pathophysiology or etiology, thus constituting LOS an etiologically and mechanistically distinct group of patients [5].

Several approaches are possible when trying to answer these questions and those require studies taking into account specific ages of onset of Schizophrenia (in this case >40 years old vs <40 years of age). Possible approaches would be the search for resemblances and differences between their risk and protective factors, neuro-imaging abnormalities, clinical course of disease and statistical association with organic CNS disease (not typical of EOS). The neuroimaging approach was already briefly mentioned and we found it prudent not to discuss comparative pathophysiology based on this parameter because many of the neuroimaging abnormalities have an unclear pathological role and uncertain cause-effect relationship.

The hypothesis of LOS being a delayed form of EOS would make pertinent the search for protective/delaying factors of Schizophrenia. Some risk factors and delaying factors for Schizophrenia have emerged and will be discussed hereafter.

LOS known risk and delaying factors

Risk Factors

The importance of studying the risk factors for LOS (and Schizophrenia in general) derives not only from identifying potentially predictive, modifiable and avoidable factors, but also from the need for a etiopathogenic point of view (essential for studying better treatment targets). The degree of risk factors' overlap between EOS and LOS could give hints to the degree of overlap between their etiopathogenies: similar risk factors would point LOS more as a delayed form of EOS and different risk factors would suggest alternative/additional etiopathogenic mechanisms leading to LOS.

The only study that systematically reviewed risk factors specifically for LOS patients concluded that the strongest predictors were: (1) history of psychotic symptoms, (2) cognitive deficits, (3) poor health status, (4) visual impairment, and (5) negative life events; older age, female gender, most socio-demographic indicators, premorbid personality traits, positive psychiatric history, substance-related disorders, and hearing impairment were not associated with psychosis in older patients [11]. A cohort study based on child survivors of the Holocaust also suggests an influence of stress exposure to LOS cases [43]. Social isolation that precedes LOS may be a prodromal phase instead of a risk factor, as behavioral studies from ablation studies suggest that it may be early manifestations of uncal pathology [44].

Hormonal changes, neuropsychological alterations, and abnormal findings on brain imaging may also be important risk factors, however they are not well studied on a longitudinal basis [11]. Thus, these data demonstrated that there seems not to be an entire overlap between EOS and LOS risk factors, presented by the lack of association between LOS and premorbid personality traits, positive psychiatric history and substance-related disorders. However, from a mechanistic point of view, this data has to be interpreted with caution since theoretically different factors may act through similar targets, perturbing the same pathologically-relevant processes.

On the genetic level, some molecular factors have recently emerged. One biologic risk factor is worthy of note since that it constitutes the only biological factor specifically associated with LOS and not with EOS: chemokine receptor type 5 (CCR5)* 32-bp deletion allele. We emphasize that this genetic risk factor is associated to LOS when comparing to both general population and early-onset cases.

CCR5 is an immunological receptor and binds a considerable number of chemokines. It is also the major co-receptor for the macrophage - infecting strains of HIV and is associated with several immune-mediated diseases [45].

In the brain, the expression of CCR5 varies with developmental stage, cell type, and brain region [46]. Besides that, chemokines and their receptors have been implicated in a variety of normal functions in the brain including neurodevelopment, neuronal survival and intercellular communication [46]. Accordingly, abnormalities in chemokine functions may predispose for Schizophrenia and other psychiatric illnesses. In support of this, psychiatric changes such as psychotic Schizophrenia-like manifestations have been observed in humans upon treatment with cytokines [16, 45, 46]. Moreover, some studies have revealed abnormalities in the secretion and blood levels of cytokines in Schizophrenia patients. Additionally, disturbances in chemokine

* [EMBL: ENSG00000160791]

levels can be induced by infectious agents. In prenatal life or early childhood, this might have a profound effect on the development of some brain functions. In fact, the increased risk for Schizophrenia in adulthood associated with prenatal exposure to common viruses could be a consequence of cytokine disturbances induced by these. A retroviral etiology of Schizophrenia has also been suggested based on recent observations that discovered retroviral transcripts in cerebrospinal fluid from Schizophrenia patients [16, 45, 46].

It is possible that the deletion allele is a modulating factor that protects against the generally more severe forms of EOS in individuals predisposed for psychotic illnesses. Such protection could stem from an altered cytokine response to common viruses back in early childhood or prenatal life. If so, this may reflect a decreased ability of the deletion allele for clearance of common infections, leading to neuronal damages and predisposition for a specific form of Schizophrenia with a late onset. Interactions between CCR5 and viruses possessing a potential for establishing persistent infections with long latency periods such as retroviruses could be of particular interest in this respect.

The fact that this genetic risk factor is associated to LOS when comparing to both general population and early-onset cases, suggests that this receptor may be involved in pathologic mechanisms of LOS not shared with EOS. Interestingly, as CCR5 is associated with neurodevelopment, neuronal survival and intercellular communication, this resembles the same processes attributed to the pathogenesis of EOS and hence this may indicate that LOS may use alternative but confluent pathologic pathways to generate the schizophrenic syndrome. Worthy of note, despite CCR5 deletion allele in not associated with Schizophrenia when patients are analyzed regardless of age of onset. Hence, it constitutes a risk factor specific for later forms of

Schizophrenia and has a simultaneous pathologic and delaying role for LOS, suggesting pathophysiologic proximity to the pathological processes underlying the development of LOS.

Delaying factors

The search for delaying factors of onset of Schizophrenia might have implications on knowledge of new therapeutic targets in patients or high-risk individuals, and also elucidate about potential evitable factors, and so, a way to delay the disorder.

Moreover, to ascertain whether or not there are factors associated with a higher age of onset of symptoms constitutes another way to study the hypothesis of LOS being/having a component of a delay in pathological processes characteristic of EOS. A considerable amount of studies ascertained the existence of such factors and have demonstrated the existence of multiple factors, environmental or genetic, associated with a later onset of the disorder. These delaying factors may be divided in two types: (1) delaying factors with effect in the susceptibility to Schizophrenia and (2) delaying factors not influencing that risk. The simultaneous effect on both age of onset and the susceptibility to the disorder suggests a role of these factors and respective pathways in the pathogenic mechanisms underlying Schizophrenia.

However, as the populations studied are basically EOS-cases, the studies on this subject only associate environmental or biologic factors with age within the EOS-group itself. Hence, it would be of great importance to study if these factors delay the onset of symptoms enough time so that its carriers are over-represented in the LOS group; in other words, if there is an association of these factors with LOS relative to EOS-cases

and the healthy population. By now it is pertinent to speculate that individuals who carry some of these factors (with or without a role in susceptibility) may be the ones who develop symptoms later in life and come to be diagnosed with LOS. However, if LOS is only a delayed form of EOS, it is expected that besides the delaying factors, the genetic aggregation and susceptibility remains equal. In fact, as already mentioned, LOS has a lower association to family history of Schizophrenia than EOS-cases, which points otherwise. So, if delaying factors explain the origin of LOS, some of them would have to play a protective role as well. Alternatively, they may explain only a fraction of LOS cases.

As it is not conceivable to discuss exhaustively each one of the factors that our search found to be associated with later age of onset, we chose to select and discuss one factor that appeared to us to be the most compelling: the female gender. It is a factor associated with later onset of symptoms within the group of EOS-patients, it is over-represented in LOS relative to male gender, which contrasts strongly with male predominance in EOS [5, 13, 17, 20]. Besides, female gender is associated with less severity of symptoms independently of the age of diagnosis. This may suggest that in some female susceptible individuals their gender may suffice to delay the initial manifestation until after 40 years old, when they are classified as LOS-patients; and/or the differences between genders might imply distinct etiopathological processes [17]. Some data points to the former notion and will be discussed hereafter.

Studies based on different cultures found that female gender is associated with later onset, different content of delusions, less negative symptoms, more affective symptoms, lower average daily dose of antipsychotics, less co-morbid cigarette smoking, alcohol and drugs consumption and course of illness more favorable (short and mild terms), although they tend to exhibit a poorer outcome in the VLOSP cases,

particularly in terms of clinical course, longest episode and remission type [5, 17, 21]. This gender phenomenon is not readily explicable by women and the older patients being more inclined to consult or be directed toward a mental professional [5, 11]. Excluding the data concerning gender in VLOSP cases, the remaining data constitute a rational base to view female gender as a strong delaying factor in Schizophrenia development although it is not a protective one given that there´s no predominance of either gender when analyzing Schizophrenia independently of age of diagnosis.

Given the facts above, it becomes tempting to explore the role(s) of female hormones in CNS. Also, the data above has served as rationale for experimental treatment of LOS-patients with female hormones, specifically estrogens, as already mentioned. In fact, several studies provided different lines of evidence relative to female hormones, which were pertinently reviewed by some articles and that may be schematized as follows: (1) epidemiological studies showed that young women are less likely to develop Schizophrenia than men of the same age; (2) women are more likely to develop LOS after menopause; (3) clinical studies showed higher psychotic symptoms in perimenopausal women; and (4) women at the low estrogen phase of the menstrual cycle tend to experiment worsening of psychotic symptoms; (5) Three randomized double-blind placebo-controlled trials and an open-label showing that adding estradiol to women's usual antipsychotic medications was associated with significant abatement of Schizophrenia symptoms; (6) A small study of men with Schizophrenia who received oral estradiol valerate showing a significant abatement in psychotic symptoms; (7) A case reporting estrogen replacement therapy alone producing remission of symptoms in a periclimacteric patient with LOS experiencing severe first-rank symptoms [37, 38].

Estrogens have some well-known effects in the CNS which include significant effect on modulation of dopamine and serotonin receptors, very important targets of the

antipsychotic drugs prescribed to schizophrenic patients and responsible for remission of the symptoms to the premorbid phase, as previously noted [21, 47]. So, estrogens have significant modulation of important effectors and pathways that seem to be extremely important to Schizophrenia syndrome.

The gender differences in age of onset and clinical characteristics have been postulated to be due to an antipsychotic effect of estrogens. The estrogen hypothesis postulates that estrogen exerts a protective effect in schizophrenic women, suggesting that estradiol has specific antipsychotic-like effects on the symptoms of Schizophrenia, and an estrogen supplement might be particularly effective in the treatment and prophylaxis in women with LOS [38].

Therefore, women with a genetic vulnerability for psychotic disorder might be protected when they are younger, but develop psychotic disorder of a chronic type when their vulnerability becomes expressed later in life, under the influence of, for example, neurodegenerative mechanisms. On the other hand, genetically vulnerable men will be more likely to express their liability at an earlier age. Consequently, only men with lower levels of vulnerability develop psychotic disorders in old age, therefore displaying better outcome than their female counterparts [21]. Although this estrogen hypothesis may have some utility in explaining differences in mean age of onset and the second incidence peak in middle-aged women, it cannot explain gender differences in older age groups [21].

Interestingly, the tendency to overrepresentation of women in LOS dissipated when only the cases with a positive family history of Schizophrenia or other psychotic disorder were selected, suggesting that characteristic associated with the female gender may be ineffective in a background of strong individual susceptibility [17].

Interestingly, a recent work studied the effect of different genotypes for the promoter o Neuropeptide Y, a neurotransmitor found dimished in postmortem brains of schizophrenic patients, on the susceptibility to develop Schizophrenia (independently of age of onset) [48]. Accordingly to their primary hypothesis, they verified that -485 T polymorphism, associated with less transcription of the gene, was associated with Schizophrenia susceptibility. Surprisingly, they found simultaneously an inverse correlation of -485 T polymorphism with symptom severity in a dose-effect fashion (homozygotes being the less symptomatic patients). Also, in the homozygote group of schizophrenic patients, a bi-modal distribution of ages of onset was present, with some developing EOS and others, especially women, having disease onset after 40 years of age, which contrasted with single peaks of onset of wild type genotypes and heterozygote genotype. Finally, they verified that schizophrenic symptoms developing below 15 years of age was highest within individuals with wild-type genotypes and totally absent in homozygotes for the mentioned polymorphism, further emphasizing this delaying effect. The findings of this study may have several implications in future research in the area of Schizophrenia: (1) analysis of individual susceptibility factors seems to be an entirely distinct parameter, namely independent of clinical severity and age of onset; (2) – the interaction of delaying factors (i.e. NPY seems to be), namely with the feminine sex, may suffice to delay diagnosis after 40 years of age; (3) – association of NPY with Schizophrenia independently of age of onset of symptomatology seems to support mechanistic overlapping between EOS and LOS.

An important and complementary study of the hypothesis of LOS group including some delayed EOS cases would be analyzing specifically LOS patients and verify if there is an excess of the delaying factors in these groups when comparing to healthy population and EOS-cases, compatible with the hypothesis of delaying. Also, to

verify if this patients exhibit simultaneously aggregation to the same polymorphism well established to be associated with typical cases of Schizophrenia with be compatible with the same general hypothesis. One good example is to examine if LOS group is associated with the same polymorphisms well established to be associated with EOS and which constitute the rationale for the viewing of EOS as a neurodevelopmental disease, in example, polymorphisms of neuroregulin and dysbindin [8]. This study, which we think of great importance to the question of etiopathogeny of LOS relative to that of EOS, is not done yet

Association of LOS with CNS diseases:

Cerebrovascular pathology and Neurodegenerative Disease

It is worth noting that LOS-cases stand chronologically between a form of Schizophrenia that has been non-lesional by definition (EOS) and the so-called VLOSP form, strongly associated with CNS lesions with plausible pathologic role leading to psychotic symptoms, those including ischemic, tumoral or other neurodegenerative conditions [49]. Conditions that rarely mimic Schizophrenia in early ages and that must be excluded before diagnosing EOS include head trauma, infections, brain tumors, seizures, multiple sclerosis, and Wilson's disease, endocrinopathies, autoimmune disorders, vitamin deficiencies and adverse reactions to prescribed medication [50]. Thus, a variety of secondary conditions have been proved to be associated with the schizophrenic syndrome in early ages as in older ages, although rare in the former. From this perspective, is LOS more similar to EOS or is it more similar to VLOSP in terms of association with CNS (primary or secondary) pathologic conditions? This question is not solved by the already-mentioned resemblances in neuroimaging between EOS and

LOS, once the processes that underlie these changes may have different natures. Moreover, there are anatomo-pathological findings in LOS that overlap with those characteristic of some neurodegenerative disorders [51, 52].

The resolution of the previous question finds its importance both in the clinical and etiopathogenic perspectives. On one hand, from a etiopathogenic point of view, studying the association of LOS with lesional processes may constitute another clue to the origin of this group of patients, namely if it constitutes a delayed form of the "non-organic" EOS (if LOS is not associated with neurodegenerative conditions) or, alternatively, an heterogeneous group made of delayed cases and patients suffering from diseases affecting the CNS (not necessarily affecting distinct pathways involved in EOS forms).

On the other hand, from the clinical point of view, a possible association of LOS with degenerative processes in the CNS would raise the possibility that Schizophrenia syndrome in later age constituting a symptom of neurodegenerative diseases and bring a prodrome of dementia in those disease-contexts. If LOS is associated with dementia that would be either because of association with dementiating diseases (pure statistical aggregation or LOS constituting a symptom group in those diseases) or through some of its underlying process converge/are shared with CNS degenerative dementiating diseases: LOS as cause of dementia vs LOS as a manifestation of neurodegenerative diseases.

Scarce amount of data is available to give a solid answer when studying aggregation of LOS with common neurodegenerative pathologies. Nevertheless, we´ll review data concerning possible association of LOS with cardiovascular disease and primary neurodegenerative diseases like Alzheimer disease (AD), Fronto-temporal

dementia (FTD), Lewis Bodies dementia, Parkinson's disease (PD) and Neurofibrillary Tangles-predominant senile dementia (NFT-SD).

LOS and Cerebrovascular disease

As already mentioned, VLOSP cases exhibit high association with CNS lesions, and these include cerebrovascular disease, local thrombosis or embolus. In fact, in a wider view, several neuropsychiatric disorders such as mood, anxiety and psychotic disorders occur following cerebrovascular lesions. Thus, it is pertinent to study if such association is also present in the LOS cases and, if so, in what extent.

There is considerable evidence that LOS-patients tend to have high cardiovascular risk profile [53]. Also, psychotic symptoms are prevalent among people with cerebrovascular disease [49]. Despite those facts, works available are not concordant in their findings relative to the relationship between situations of cerebral hypoperfusion and LOS, with some studies that used a neuroimaging approach finding large areas of subcortical hyperintensities in patients with LOS and others finding no differences when comparing to healthy age-matched subjects [54, 55]. Interestingly, the studies that found association with acute or chronic ischemic disorders found also strong relation with disturbance of the right side of the brain.

A recent work has analyzed a possible pathogenic role of extracranial arterial pathology in Late-Onset Psychiatric disorders [53]. This study has found association of LOS with both chronic insufficient cerebral blood flow and thromboembolic complications, symptomatic or clinically silent, of carotid or vertebral atherosclerotic disease. The plausibility for a cause-effect relationship is emphasized by the fact that these disorders may be solved with vascular reconstruction [56, 57].

LOS, Neurodegenerative diseases and Dementia

As in the case of cerebrovascular disease, psychotic symptoms are common in some prevalent neurodegenerative diseases, like AD, Lewis Bodies` dementia, PD and FTD [49, 52]. However, studies made so far, although not unanimously, have failed to demonstrate any association of LOS with AD, Lewis Bodies and PD [51, 58, 59]. Thus, if the hypothesis of LOS being associated with dementia, as already debated, is found to be a true association, this seems not to be due to LOS being statistically associated or being a prodrome of dementia in these disease-contexts, since it has no relation to them. If LOS may constitute a prodrome of dementia in other specific pathologic situations, e.g. a form of presentation of some diseases evolving to dementia, is somewhat different. Of particular interest is a possible association of LOS with two specific forms of dementia, the FTD, in which frontotemporal lobar degeneration occurs and NFT-SD [44, 52]. It is not known if these degenerative diseases are associated or not with LOS but anatomopathological studies in dementiated LOS patients showed some similarities with lesions found tipically with patients with FTP and NFT-SD. IN the case of NFT-SD, the presence of neurofibrillary tangles was described in LOS, predominating in the entorhinal cortex, a neuroanatomic site already implicated in LOS in what concerns to memory impairment, affective and positive symptoms, without markedly affecting the personality [44]. Relative to FTP, it has been investigated if FTD-like neuropathological changes are present in Schizophrenia. TAR DNA-binding protein 43 (TDP 43), an mRNA-binding protein normally present in the nucleus and absent in neuronal nucleus of FTD patients was also found to absent from the nucleus of patients with LOS [52]. Since the known functions of this protein include regulation of gene expression (at levels of transcription and translation) and the modulation of neural plasticity through

dendritic spine growth, this could have a role in the pathogenesis of LOS, namely in what may lead to dementia in these patients [52]. The significance of these findings relates with two questions: a possible coexistence of LOS with these disease entities or, alternatively, pathogenic mechanisms of LOS similar in some features to some neurodegenerative diseases. However, one has to emphasize that anatomopatholigic studies comparing LOS with NFT-SD and FTP are based in series of cases and so it is premature to make conclusions in the current state of knowledge before larger casuistic are analyzed.

Conclusions

- There are still great difficulties in the research about LOS because of discrepancy in the terminology and criteria used to define it, poor research using this specific population and lack of uniformity in the methods used to assess these patients and analyze data.
- There are well-established differences in clinical features between LOS and EOS patients, namely predominance of female gender, less family history, less premorbid personality, less severe symptomology, less dosage of neuroleptics required to achieve a same symptomatic remission. These well-established differences give clinical utility to this subdivision of Schizophrenia.
- Currently there is not enough data to describe the cognitive evolution in LOS.
- Concerning etiopathogeny, current evidence support both the notions of LOS patients being those carrying delaying factors for EOS, like female gender and

the recent found -485 T promoter polymorphism of NPY, and that LOS may have its own pathogenic mechanisms.

- The evidence for mechanistic overlap lies mainly in clinical resemblances between LOS and EOS. Findings that support discrepant mechanisms (not necessarily affecting different neuroanatomic bases) include recent findings that associate LOS (and not EOS) with specific alleles, like 32-bp delection allele of CCR5.
- One recent review article found association of LOS with both chronic insufficient cerebral blood flow and thromboembolic complications, symptomatic or clinically silent, of carotid or vertebral atherosclerotic disease.
- Currently there is no evidence that LOS may be neither a symptom of neurodegenerative disease nor a prodrome of dementia in these contexts.
- Given the possibility of LOS constituting a heterogeneous group made up by delayed EOS cases and by distinct pathophysiologic entities, more associative studies analyzing this specific group are justified. Hence, subdivision of LOS proposed by the International Consensus remains unclear about etiopathogenic validity.

List of abbreviations

AD: Alzheimer's Disease

CCR5: Chemokine Receptor type 5

CNS: Central Nervous System

DSM: Diagnostic and Statistical Manual of Mental Disorders

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision

EOS: Early-Onset Schizophrenia

FTD: Fronto-Temporal Dementia

ICD: International Classification of Diseases

ICD-10: International Classification of Diseases, 10th revision

LOS: Late-Onset Schizophrenia

NFT: Neurofibrillary Tangles

NFT-SD: Neurofibrillary Tangles-predominant Senile Dementia

NPY: Neuropeptide Y

PD: Parkinson´s Disease

TDP-43: TAR DNA Binding Protein 43

VLOSP: Very-Late-Onset Schizophrenia-Like Psychosis

Competing interests

None known.

References

1. Cannon M, Jones P, Huttunen MO, Tanskanen A, Huttunen T, Rabe-Hesketh S, Murray RM: **School performance in Finnish children and later development of schizophrenia: a population-based longitudinal study**. *Arch Gen Psychiatry* 1999, **56**(5):457-463.
2. Harris MJ, Jeste DV: **Late-onset schizophrenia: an overview**. *Schizophr Bull* 1988, **14**(1):39-55.
3. Cervantes AN, Rabins PV, Slavney PR: **Onset of schizophrenia at age 100**. *Psychosomatics* 2006, **47**(4):356-359.
4. Bleuler M: **Clinical Picture of the late Schizophrenia**. *Fortschr Neurol P I* 1943, **15**(9):259-290.
5. Howard R, Rabins PV, Seeman MV, Jeste DV: **Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. The International Late-Onset Schizophrenia Group**. *Am J Psychiatry* 2000, **157**(2):172-178.
6. American Psychiatric Association., American Psychiatric Association. Task Force on DSM-IV.: *Diagnostic and statistical manual of mental disorders : DSM-IV-TR*. 4th edition. Washington, DC: American Psychiatric Association; 2000.
7. World Health Organization.: *The ICD-10 classification of mental and behavioural disorders : diagnostic criteria for research*. Geneva: World Health Organization; 1993.
8. Owen MJ, Williams NM, O'Donovan MC: **The molecular genetics of schizophrenia: new findings promise new insights**. *Mol Psychiatry* 2004, **9**(1):14-27.
9. Girard C, Simard M: **Clinical characterization of late- and very late-onset first psychotic episode in psychiatric inpatients**. *Am J Geriatr Psychiatry* 2008, **16**(6):478-487.
10. Vahia IV, Palmer BW, Depp C, Fellows I, Golshan S, Kraemer HC, Jeste DV: **Is late-onset schizophrenia a subtype of schizophrenia?** *Acta Psychiatr Scand* 2010, **122**(5):414-426.
11. Brunelle S, Cole MG, Elie M: **Risk factors for the late-onset psychoses: a systematic review of cohort studies**. *Int J Geriatr Psychiatry* 2012, **27**(3):240-252.
12. Rajji TK, Ismail Z, Mulsant BH: **Age at onset and cognition in schizophrenia: meta-analysis**. *Br J Psychiatry* 2009, **195**(4):286-293.
13. Casanova MF: **The pathology of paraphrenia**. *Curr Psychiatry Rep* 2010, **12**(3):196-201.
14. Quin RC, Clare L, Ryan P, Jackson M: **'Not of this world': the subjective experience of late-onset psychosis**. *Aging Ment Health* 2009, **13**(6):779-787.
15. Girard C, Simard M, Noiseux R, Laplante L, Dugas M, Rousseau F, Gagnon N, Primeau F, Keller E, Bernier PJ: **Late-onset-psychosis: cognition**. *Int Psychogeriatr* 2011, **23**(8):1301-1316.
16. Rasmussen HB, Timm S, Wang AG, Soeby K, Lublin H, Fenger M, Hemmingsen R, Werge T: **Association between the CCR5 32-bp deletion allele and late onset of schizophrenia**. *Am J Psychiatry* 2006, **163**(3):507-511.

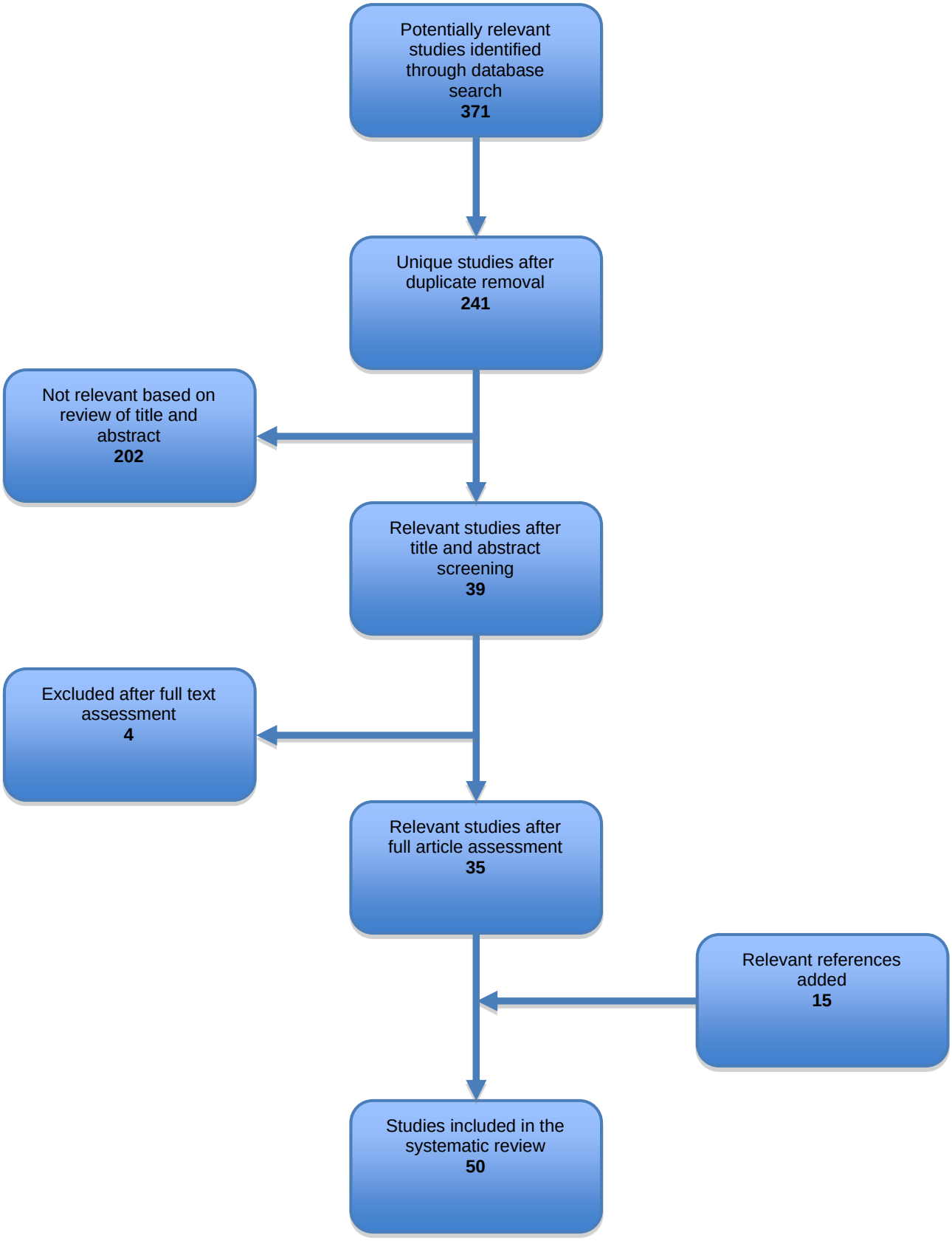
17. Tang YL, Gillespie CF, Epstein MP, Mao PX, Jiang F, Chen Q, Cai ZJ, Mitchell PB: **Gender differences in 542 Chinese inpatients with schizophrenia**. *Schizophr Res* 2007, **97**(1-3):88-96.
18. Harvey PD, Reichenberg A, Bowie CR: **Cognition and aging in psychopathology: focus on schizophrenia and depression**. *Annu Rev Clin Psychol* 2006, **2**:389-409.
19. Roth M, Morrissey JD: **Problems in the diagnosis and classification of mental disorder in old age; with a study of case material**. *J Ment Sci* 1952, **98**(410):66-80.
20. Mitter P, Reeves S, Romero-Rubiales F, Bell P, Stewart R, Howard R: **Migrant status, age, gender and social isolation in very late-onset schizophrenia-like psychosis**. *Int J Geriatr Psychiatry* 2005, **20**(11):1046-1051.
21. Kohler S, van der Werf M, Hart B, Morrison G, McCreadie R, Kirkpatrick B, Verkaaik M, Krabbendam L, Verhey F, van Os J *et al*: **Evidence that better outcome of psychosis in women is reversed with increasing age of onset: a population-based 5-year follow-up study**. *Schizophr Res* 2009, **113**(2-3):226-232.
22. Korner A, Lopez AG, Lauritzen L, Andersen PK, Kessing LV: **Late and very-late first-contact schizophrenia and the risk of dementia--a nationwide register based study**. *Int J Geriatr Psychiatry* 2009, **24**(1):61-67.
23. Hassett A: **A descriptive study of first presentation psychosis in old age**. *Aust N Z J Psychiatry* 1999, **33**(6):814-824.
24. Wynn Owen PA, Castle DJ: **Late-onset schizophrenia: epidemiology, diagnosis, management and outcomes**. *Drugs Aging* 1999, **15**(2):81-89.
25. Pearlson GD, Kreger L, Rabins PV, Chase GA, Cohen B, Wirth JB, Schlaepfer TB, Tune LE: **A chart review study of late-onset and early-onset schizophrenia**. *Am J Psychiatry* 1989, **146**(12):1568-1574.
26. Jeste DV, Harris MJ, Krull A, Kuck J, McAdams LA, Heaton R: **Clinical and neuropsychological characteristics of patients with late-onset schizophrenia**. *Am J Psychiatry* 1995, **152**(5):722-730.
27. Howard R, Castle D, Wessely S, Murray R: **A comparative study of 470 cases of early-onset and late-onset schizophrenia**. *Br J Psychiatry* 1993, **163**:352-357.
28. Scott J, Greenwald BS, Kramer E, Shuwall M: **Atypical (second generation) antipsychotic treatment response in very late-onset schizophrenia-like psychosis**. *Int Psychogeriatr* 2010:1-7.
29. Granholm E, McQuaid JR, McClure FS, Pedrelli P, Jeste DV: **A randomized controlled pilot study of cognitive behavioral social skills training for older patients with schizophrenia**. *Schizophr Res* 2002, **53**(1-2):167-169.
30. Poulet E, Brunelin J, Kallel L, D'Amato T, Saoud M: **Maintenance treatment with transcranial magnetic stimulation in a patient with late-onset schizophrenia**. *Am J Psychiatry* 2008, **165**(4):537-538.
31. Folsom DP, Lebowitz BD, Lindamer LA, Palmer BW, Patterson TL, Jeste DV: **Schizophrenia in late life: emerging issues**. *Dialogues Clin Neurosci* 2006, **8**(1):45-52.
32. Allebeck P: **Schizophrenia: a life-shortening disease**. *Schizophr Bull* 1989, **15**(1):81-89.
33. Mortensen PB, Juel K: **Mortality and causes of death in schizophrenic patients in Denmark**. *Acta Psychiatr Scand* 1990, **81**(4):372-377.

34. Chua WL, de Izquierdo SA, Kulkarni J, Mortimer A: **Estrogen for schizophrenia**. *Cochrane Database Syst Rev* 2005(4):CD004719.
35. Bergemann N, Mundt C, Parzer P, Pakrasi M, Eckstein-Mannsperger U, Haisch S, Salbach B, Klinga K, Runnebaum B, Resch F: **Estrogen as an adjuvant therapy to antipsychotics does not prevent relapse in women suffering from schizophrenia: results of a placebo-controlled double-blind study**. *Schizophr Res* 2005, **74**(2-3):125-134.
36. Louza MR, Marques AP, Elkis H, Bassitt D, Diegoli M, Gattaz WF: **Conjugated estrogens as adjuvant therapy in the treatment of acute schizophrenia: a double-blind study**. *Schizophr Res* 2004, **66**(2-3):97-100.
37. Kulkarni J: **Oestrogen--a new treatment approach for schizophrenia?** *Med J Aust* 2009, **190**(4 Suppl):S37-38.
38. Bergemann N, Abu-Tair F, Strowitzki T: **Estrogen in the treatment of late-onset schizophrenia**. *J Clin Psychopharmacol* 2007, **27**(6):718-720.
39. Rakesh G, Rao NP, Venkatasubramanian G, Behere RV, Varambally S, Gangadhar BN: **Treatment with phytoestrogens for depressive symptoms in late-onset schizophrenia:a case report**. *Prim Care Companion CNS Disord* 2011, **13**(3).
40. Huang C, Zhang YL: **Clinical differences between late-onset and early-onset chronically hospitalized elderly schizophrenic patients in Taiwan**. *Int J Geriatr Psychiatry* 2009, **24**(10):1166-1172.
41. Palmer BW, Bondi MW, Twamley EW, Thal L, Golshan S, Jeste DV: **Are late-onset schizophrenia spectrum disorders neurodegenerative conditions? Annual rates of change on two dementia measures**. *J Neuropsychiatry Clin Neurosci* 2003, **15**(1):45-52.
42. Mitford E, Reay R, McCabe K, Paxton R, Turkington D: **Ageism in first episode psychosis**. *Int J Geriatr Psychiatry* 2010, **25**(11):1112-1118.
43. Reulbach U, Bleich S, Biermann T, Pfahlberg A, Sperling W: **Late-onset schizophrenia in child survivors of the holocaust**. *J Nerv Ment Dis* 2007, **195**(4):315-319.
44. Casanova MF: **The role of the entorhinal cortex in paraphrenia**. *Curr Psychiatry Rep* 2010, **12**(3):202-207.
45. Mueller A, Strange PG: **The chemokine receptor, CCR5**. *Int J Biochem Cell Biol* 2004, **36**(1):35-38.
46. Westmoreland SV, Alvarez X, deBakker C, Aye P, Wilson ML, Williams KC, Lackner AA: **Developmental expression patterns of CCR5 and CXCR4 in the rhesus macaque brain**. *J Neuroimmunol* 2002, **122**(1-2):146-158.
47. Riecher-Rossler A, de Geyter C: **The forthcoming role of treatment with oestrogens in mental health**. *Swiss Med Wkly* 2007, **137**(41-42):565-572.
48. Doi N, Itokawa M, Hoshi Y, Arai M, Furukawa A, Ujike H, Sora I, Yoshikawa T: **A resistance gene in disguise for schizophrenia?** *Am J Med Genet B Neuropsychiatr Genet* 2007, **144B**(2):165-173.
49. Reeves RR, Brister JC: **Psychosis in late life: emerging issues**. *J Psychosoc Nurs Ment Health Serv* 2008, **46**(11):45-52.
50. Doran AR, Breier A, Roy A: **Differential diagnosis and diagnostic systems in schizophrenia**. *Psychiatr Clin North Am* 1986, **9**(1):17-33.
51. Lagodka A, Robert P: **[Is late-onset schizophrenia related to neurodegenerative processes? A review of literature]**. *Encephale* 2009, **35**(4):386-393.

52. Velakoulis D, Walterfang M, Mocellin R, Pantelis C, Dean B, McLean C: **Abnormal hippocampal distribution of TDP-43 in patients with-late onset psychosis**. *Aust N Z J Psychiatry* 2009, **43**(8):739-745.
53. van der Heijden FM, Zeebregts CJ, Reijnen MM: **Does extracranial arterial pathology play a role in late-onset psychiatric disorders?** *Cogn Behav Neurol* 2010, **23**(3):147-151.
54. Stern Y, Albert M, Brandt J, Jacobs DM, Tang MX, Marder K, Bell K, Sano M, Devanand DP, Bylsma F *et al*: **Utility of extrapyramidal signs and psychosis as predictors of cognitive and functional decline, nursing home admission, and death in Alzheimer's disease: prospective analyses from the Predictors Study**. *Neurology* 1994, **44**(12):2300-2307.
55. Tonkonogy JM, Geller JL: **Late-onset paranoid psychosis as a distinct clinicopathologic entity: magnetic resonance imaging data in elderly patients with paranoid psychosis of late onset and schizophrenia of early onset**. *Neuropsychiatry Neuropsychol Behav Neurol* 1999, **12**(4):230-235.
56. Donovan AL, Freudenreich O: **Resolution of late-onset hypomania after repair of carotid artery stenosis: a case of vascular hypomania**. *J Clin Psychiatry* 2007, **68**(5):798.
57. Coumans JV, McGrail KM: **Psychiatric presentation of carotid stenosis**. *Surgery* 2000, **127**(6):713-715.
58. Howard RJ, Graham C, Sham P, Dennehey J, Castle DJ, Levy R, Murray R: **A controlled family study of late-onset non-affective psychosis (late paraphrenia)**. *Br J Psychiatry* 1997, **170**:511-514.
59. Brodaty H, Sachdev P, Rose N, Rylands K, Prenter L: **Schizophrenia with onset after age 50 years. I: Phenomenology and risk factors**. *Br J Psychiatry* 1999, **175**:410-415.
60. Dupont RM, Lehr PP, Lamoureaux G, Halpern S, Harris MJ, Jeste DV: **Preliminary report: cerebral blood flow abnormalities in older schizophrenic patients**. *Psychiatry Res* 1994, **55**(3):121-130.
61. Sachdev P, Brodaty H, Rose N, Haindl W: **Regional cerebral blood flow in late-onset schizophrenia: a SPECT study using 99mTc-HMPAO**. *Schizophr Res* 1997, **27**(2-3):105-117.
62. Glorioso C, Sibille E: **Between destiny and disease: genetics and molecular pathways of human central nervous system aging**. *Prog Neurobiol* 2011, **93**(2):165-181.

Figures

Figure 1 - Flow chart of systematic review



Tables

Table 1 - DSM-IV-TR Diagnostic Criteria for Schizophrenia

A. Characteristic symptoms of the active phase Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated): 1. Delusions 2. Hallucinations 3. Disorganized speech (e.g., frequent derailment or incoherence) 4. Grossly disorganized or catatonic behavior 5. Negative symptoms, i.e., affective flattening, alogia, or avolition **Note:** Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.
B. Social/occupational dysfunction For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).
C. Duration Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).
D. Schizoaffective and mood disorder exclusion Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either (1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.
E. Substance/general medical condition exclusion The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.
F. Relationship to a pervasive developmental disorder If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

***Adapted from** [6]*

Table 2 - CID-10 Diagnostic Criteria for Schizophrenia

Characteristic symptoms of the active phase At least one of the following, each present for a significant portion of time during a 1-month period: 1. Thought echo, thought insertion/withdrawal/broadcast 2. Passivity, delusional perception 3. Third person auditory hallucination, running commentary 4. Persistent bizarre delusions Or Two (or more) of the following, each present for a significant portion of time during a 1-month period: 1. Persistent hallucinations 2. Thought disorder 3. Catatonic behavior 4. Negative symptoms 5. Significant behavior change
Exclusion criteria 1. Mood disorders 2. Schizoaffective disorder 3. Over brain disease 4. Drug intoxication or withdrawal

Adapted fro: *[7]*

Table 3 - Features characteristic of Late-Onset compared to Early-Onset Schizophrenia

Features in common		Features not in common
Features which are commoner	**Features which are less common or less severe**	
1. Visual, tactile, and olfactory hallucinations 2. Third person, running commentary, derogatory auditory hallucinations 3. Persecutory delusions 4. Partition delusions	1. Formal thought disorder (rare if onset >60 years) 2. Affective flattening 3. Affective blunting 4. Negative symptoms (rare if onset >60 years) 5. Positive symptoms 6. Premorbid educational, occupational and psychosocial impairment 7. Cognitive impairment (working and verbal memory, process speed, perception organization, cognitive flexibility) 8. General psychopathology	1. Female predominance 2. No clear genetic loading 3. Association with sensory deficits and social isolation (if onset >60 years) 4. Lower antipsychotic dosage required 5. Better everyday functioning and health-related quality of life

Adapted from *[5, 10, 13, 60, 61]*

Table 4 - Brain Imaging characteristic of Late-Onset Schizophrenia compared to Early-Onset Schizophrenia and normal aging

Features in common with EOS	Features not in common with EOS	Features in common with Normal Aging	Features not in common with Normal Aging
1. Higher ventricle-to-brain ratio * 2. Higher third ventricle volume * 3. Reduction of the left temporal lobe* 4. Reduction of the superior temporal gyrus* 5. Later peak latency of N400 congruity effect	1. Larger thalamic volume * 2. Hypoperfusion in frontal and temporal areas	1. Larger thalamic volume *	1. Higher ventricle-to-brain ratio* 2. Higher third ventricle volume 3. Increase and no increase in D2 receptor density 4. Later peak latency of N400 congruity effect

Functional (by PET and/or SPECT) and Structural* (by TC and/or MRI) brain imaging.
Adapted from [5, 43, 62]

Normas de publicação da revista *BioMed Central Psychiatry*

Preparing main manuscript text

General guidelines of the journal's style and language are given below.

Overview of manuscript sections for Research article
Manuscripts for Research article articles submitted to *BMC Psychiatry* should be divided into the following sections (in this order):

- Title page
- Abstract
- Keywords
- Background
- Methods
- Results and discussion
- Conclusions
- List of abbreviations used (if any)
- Competing interests
- Authors' contributions
- Authors' information
- Acknowledgements
- Endnotes
- References
- Illustrations and figures (if any)
- Tables and captions
- Preparing additional files

The **Accession Numbers** of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript should be provided, in square brackets and include the corresponding database name; for example, [EMBL:AB026295, EMBL:AC137000, DDBJ:AE000812, GenBank:U49845, PDB:1BFM, Swiss-Prot:Q96KQ7, PIR:S66116]. The databases for which we can provide direct links are: EMBL Nucleotide Sequence Database (EMBL), DNA Data Bank of Japan (DDBJ), GenBank at the NCBI (GenBank), Protein Data Bank (PDB), Protein Information Resource (PIR) and the Swiss-Prot Protein Database (Swiss-Prot).
You can download a template (Mac and Windows compatible; Microsoft Word 98/2000) for your article.
For reporting standards please see the information in the About section.

Title page
The title page should:

- provide the title of the article
- list the full names, institutional addresses and email addresses for all authors
- indicate the corresponding author

Please note:

- the title should include the study design, for example "A versus B in the treatment of C: a randomized controlled trial X is a risk factor for Y: a case control study"
- abbreviations within the title should be avoided

Abstract
The Abstract of the manuscript should not exceed 350 words and must be structured into separate sections: **Background**, the context and purpose of the study; **Methods**, how the study was performed and statistical tests used; **Results**, the main findings; **Conclusions**, brief summary and potential implications. Please minimize the use of abbreviations and do not cite references in the abstract. **Trial registration**, if your Research article articles reports the results of a controlled health care intervention, please list your trial registry, along with the unique identifying number (e.g.**Trial registration**: Current Controlled Trials ISRCTN73824458). Please note that there should be no space between the letters and numbers of your trial registration number. We recommend manuscripts that report randomized controlled trials follow the CONSORT extension for abstracts.

Keywords
Three to ten keywords representing the main content of the article.

Background
The Background section should be written in a way that is accessible to researchers without specialist knowledge in that area and must clearly state - and, if helpful, illustrate - the background to the research and its aims. Reports of clinical research should, where appropriate, include a summary of a search of the literature to indicate why this study was necessary and what it aimed to contribute to the

field. The section should end with a brief statement of what is being reported in the article.

Methods
The methods section should include the design of the study, the setting, the type of participants or materials involved, a clear description of all interventions and comparisons, and the type of analysis used, including a power calculation if appropriate. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses in the Methods section.

For studies involving human participants a statement detailing ethical approval and consent should be included in the methods section. For further details of the journal's editorial policies and ethical guidelines see 'About this journal'. For further details of the journal's data-release policy, see the policy section in 'About this journal'.

Results and discussion
The Results and discussion may be combined into a single section or presented separately. Results of statistical analysis should include, where appropriate, relative and absolute risks or risk reductions, and confidence intervals. The Results and discussion sections may also be broken into subsections with short, informative headings.

Conclusions
This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance. Summary illustrations may be included.

List of abbreviations
If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations can be provided, which should precede the competing interests and authors' contributions.

Competing interests
A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organizations. Authors must disclose any financial competing interests; they should also reveal any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.

Authors are required to complete a declaration of competing interests. All competing interests that are declared will be listed at the end of published articles. Where an author gives no competing interests, the listing will read 'The author(s) declare that they have no competing interests'.

When completing your declaration, please consider the following questions:

Financial competing interests

- In the past five years have you received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? Is such an organization financing this manuscript (including the article-processing charge)? If so, please specify.
- Do you hold any stocks or shares in an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? If so, please specify.
- Do you hold or are you currently applying for any patents relating to the content of the manuscript? Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? If so, please specify.
- Do you have any other financial competing interests? If so, please specify.

Non-financial competing interests
Are there any non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript? If so, please specify.

If you are unsure as to whether you, or one your co-authors, has a competing interest please discuss it with the editorial office.

Authors' contributions
In order to give appropriate credit to each author of a paper, the individual contributions of authors to the manuscript should be specified in this section.

An 'author' is generally considered to be someone who has made substantive intellectual contributions to a published study. To qualify as an author one should 1) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) have been involved in drafting the manuscript or revising it critically for important intellectual content; and 3) have given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

We suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the

immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

All contributors who do not meet the criteria for authorship should be listed in an acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support.

Authors' information
You may choose to use this section to include any relevant information about the author(s) that may aid the reader's interpretation of the article, and understand the standpoint of the author(s). This may include details about the authors' qualifications, current positions they hold at institutions or societies, or any other relevant background information. Please refer to authors using their initials. Note this section should not be used to describe any competing interests.

Acknowledgements
Please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation. Authors must describe the role of the funding body, if any, in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Please also acknowledge anyone who contributed materials essential for the study. If a language editor has made significant revision of the manuscript, we recommend that you acknowledge the editor by name, where possible.

The role of a scientific (medical) writer must be included in the acknowledgements section, including their source(s) of funding. We suggest wording such as 'We thank Jane Doe who provided medical writing services on behalf of XYZ Pharmaceuticals Ltd.'

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

Endnotes
Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

References
All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. Each reference must have an individual reference number. Please avoid excessive referencing. If automatic numbering systems are used, the reference numbers must be finalized and the bibliography must be fully formatted before submission.

Only articles, datasets and abstracts that have been published or are in press, or are available through public e-print/preprint servers, may be cited; unpublished abstracts, unpublished data and personal communications should not be included in the reference list, but may be included in the text and referred to as "unpublished observations" or "personal communications" giving the names of the involved researchers. Obtaining permission to quote personal communications and unpublished data from the cited colleagues is the responsibility of the author. Footnotes are not allowed, but endnotes are permitted. Journal abbreviations follow Index Medicus/MEDLINE. Citations in the reference list should include all named authors, up to the first 30 before adding '*et al.*'.
Any *in press* articles cited within the references and necessary for the reviewers' assessment of the manuscript should be made available if requested by the editorial office.
Style files are available for use with popular bibliographic management software:

- BibTeX
- EndNote style file
- Reference Manager
- Zotero

Examples of the *BMC Psychiatry* reference style are shown below. Please ensure that the reference style is followed precisely; if the references are not in the correct style they may have to be retyped and carefully proofread.
All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, in the following format: **The Mouse Tumor Biology Database** [http://tumor.informatics.jax.org/mtbwi/index.do]. If an author or group of authors can clearly be associated with a web link, such as for weblogs, then they should be included in the reference.

Preparing illustrations and figures

Illustrations should be provided as separate files, not embedded in the text file. Each figure should include a single illustration and should fit on a single page in portrait format. If a figure consists of separate parts, it is important that a single composite illustration file be submitted which contains all parts of the figure. There is no charge for the use of color figures.

Formats

The following file formats can be accepted:

- EPS (preferred format for diagrams)
- PDF (also especially suitable for diagrams)
- TIFF
- PNG (preferred format for photos or images)
- Microsoft Word (version 5 and above; figures must be a single page)
- PowerPoint (figures must be a single page)
- JPEG
- BMP

Figure size and resolution

Figures are resized during publication of the final full text and PDF versions to conform to he BioMed Central standard dimensions, which are detailed below.

Figures on the web:

- width of 600 pixels (standard), 1200 pixels (high resolution).

Figures in the final PDF version:

- width of 85 mm for half page width figure;
- width of 170 mm for full page width figure;
- maximum height of 225 mm for figure and legend;
- image resolution of approximately 300 dpi (dots per inch) at the final size.

Illustrations should be designed such that all information is legible at these dimensions. All lines should be wider than 0.5 pt when constrained to standard figure widths. Authors are prompted on submission to specify the width of each figure in the final PDF (half a page wide, or a full page wide); there may be some occasions where the Production team choose to lay these out at a different width for improved legibility or consistency.

Fonts

- BioMed Central recommends the use of either Arial or Helvetica fonts using 12pt characters for text within figures.
- Courier may also be used if a monospaced font is required (for example, in sequence alignments).
- Where Greek, mathematical or other special characters are needed and cannot be inserted in Arial or Helvetica, Symbol or Mathematical PI is recommend.
- Text should be designed to be legible when the illustration is resampled to BioMed Central's standard sizes listed above.
- All fonts should be embedded.

Figure legends

The legends should be included in the main manuscript text file at the end of the document, rather than being a part of the figure file. For each figure, the following information should be provided: Figure number (in sequence, using Arabic numerals - i.e. Figure 1, 2, 3 etc); short title of figure (maximum 15 words); detailed legend, up to 300 words.

Please note that it is the responsibility of the author(s) to obtain permission from the copyright holder to reproduce figures or tables that have previously been published elsewhere.

Preparing a personal cover page

If you wish to do so, you may submit an image which, in the event of publication, will be used to create a cover page for the PDF version of your article. The cover page will also display the journal logo, article title and citation details. The image may either be a figure from your manuscript or another relevant image. You must have permission from the copyright to reproduce the image. Images that do not meet our requirements will not be used.

Images must be 300dpi and 155mm square (1831 x 1831 pixels for a raster image).

Allowable formats - EPS, PDF (for line drawings), PNG, TIFF (for photographs and screen dumps), JPEG, BMP, DOC, PPT, CDX, TGF (ISIS/Draw).

Preparing tables

Each table should be numbered and cited in sequence using Arabic numerals (i.e. Table 1, 2, 3 etc.). Tables should also have a title (above the table) that summarizes the whole table; it should be no longer than 15 words. Detailed legends may then follow, but they should be

concise. Tables should always be cited in text in consecutive numerical order.

Smaller tables considered to be integral to the manuscript can be pasted into the end of the document text file, in A4 portrait or landscape format. These will be typeset and displayed in the final published form of the article. Such tables should be formatted using the 'Table object' in a word processing program to ensure that columns of data are kept aligned when the file is sent electronically for review; this will not always be the case if columns are generated by simply using tabs to separate text. Columns and rows of data should be made visibly distinct by ensuring that the borders of each cell display as black lines. Commas should not be used to indicate numerical values. Color and shading may not be used; parts of the table can be highlighted using symbols or bold text, the meaning of which should be explained in a table legend. Tables should not be embedded as figures or spreadsheet files.

Larger datasets or tables too wide for a portrait page can be uploaded separately as additional files. Additional files will not be displayed in the final, laid-out PDF of the article, but a link will be provided to the files as supplied by the author.

Tabular data provided as additional files can be uploaded as an Excel spreadsheet (.xls) or comma separated values (.csv). As with all files, please use the standard file extensions.

Preparing additional files

Although *BMC Psychiatry* does not restrict the length and quantity of data included in an article, there may still be occasions where an author wishes to provide data sets, tables, movie files, or other information as additional files. Results that would otherwise be indicated as "data not shown" can and should be included as additional files. Since many weblinks and URLs rapidly become broken, *BMC Psychiatry* requires that all supplementary data are included as additional files rather than as a link to your own website. These files can be uploaded using the 'Additional Material files' button in the manuscript submission tool.
The maximum file size for additional files is 20 MB each, and files will be virus-scanned on submission.

Additional files will be linked to the final published article in the form supplied by the author, but will not be displayed within the article. They will be made available in exactly the same form as originally provided by the authors.

If additional material is provided, please list the following information in a separate section of the manuscript text, immediately following the tables (if any):

- File name (e.g. Additional file 1)
- File format including the three-letter file extension (including name and a URL of an appropriate viewer if format is unusual)
- Title of data
- Description of data

Additional files should be named "Additional file 1" and so on and should be referenced explicitly by file name within the body of the article, e.g. 'An additional movie file shows this in more detail [see Additional file 1]'.

Additional file formats
Ideally, file formats for additional files should not be platform-specific, and should be viewable using free or widely available tools. The following are examples of suitable formats.

- Additional documentation
  - PDF (Adode Acrobat)
- Animations
  - SWF (Shockwave Flash)
- Movies
  - MOV (QuickTime)
  - MPG (MPEG)
- Tabular data
  - XLS (Excel Spreadsheet)
  - CSV (Comma separated values)

As with figure files, files should be given the standard file extensions. This is especially important for Macintosh users, since the Mac OS does not enforce the use of standard extensions. Please also make sure that each additional file is a single table, figure or movie (please do not upload linked worksheets or PDF files larger than one sheet).

Mini-websites
Small self-contained websites can be submitted as additional files, in such a way that they will be browsable from within the full text HTML version of the article. In order to do this, please follow these instructions:

1. Create a folder containing a starting file called index.html (or index.htm) in the root.
2. Put all files necessary for viewing the mini-website within the folder, or sub-folders.
3. Ensure that all links are relative (ie "images/picture.jpg" rather than "/images/picture.jpg" or "http://yourdomain.net/images/picture.jpg" or "C:\Documents and Settings\username\My Documents\mini-website\images\picture.jpg") and no link is longer than 255 characters.
4. Access the index.html file and browse around the mini-website, to ensure that the most commonly used browsers (Internet

Explorer and Firefox) are able to view all parts of the mini-website without problems, it is ideal to check this on a different machine.

5. Compress the folder into a ZIP, check the file size is under 20 MB, ensure that index.html is in the root of the ZIP, and that the file has .zip extension, then submit as an additional file with your article.

Style and language

General

Currently, *BMC Psychiatry* can only accept manuscripts written in English. Spelling should be US English or British English, but not a mixture.

There is no explicit limit on the length of articles submitted, but authors are encouraged to be concise. There is also no restriction on the number of figures, tables or additional files that can be included with each article online. Figures and tables should be numbered in the order in which they are referred to in the text. Authors should include all relevant supporting data with each article.

BMC Psychiatry will not edit submitted manuscripts for style or language; reviewers may advise rejection of a manuscript if it is compromised by grammatical errors. Authors are advised to write clearly and simply, and to have their article checked by colleagues before submission. In-house copyediting will be minimal. Non-native speakers of English may choose to make use of a copyediting service.

Abbreviations

Abbreviations should be used as sparingly as possible. They should be defined when first used and a list of abbreviations can be provided following the main manuscript text.

Typography

- Please use double line spacing.
- Type the text unjustified, without hyphenating words at line breaks.
- Use hard returns only to end headings and paragraphs, not to rearrange lines.
- Capitalize only the first word, and proper nouns, in the title.
- All pages should be numbered.
- Use the *BMC Psychiatry* reference format.
- Footnotes are not allowed, but endnotes are permitted.
- Please do not format the text in multiple columns.
- Greek and other special characters may be included. If you are unable to reproduce a particular special character, please type out the name of the symbol in full. **Please ensure that all special characters used are embedded in the text, otherwise they will be lost during conversion to PDF.**

Units

SI units should be used throughout (liter and molar are permitted, however).

Índice