DYSKINESIA IN FIRST-EPISODE SCHIZOPHRENIC PATIENTS TREATED WITH SECOND GENERATION ANTIPSYCHOTICS. ABNORMAL MOVEMENTS AND SCHIZOPHRENIA OUTCOME

Programa de Doctorat de Psiquiatria

Departament de Psiquiatria i Medicina Legal

Universitat Autònoma de Barcelona

Doctorand: *Carles Garcia-Ribera*

Directors: *Enric Álvarez Martínez*

Maria Portella Moll

Barcelona, September 2018

Abstract

Many movement abnormalities observed in schizophrenic patients are neglected, especially those in mild and moderate forms or associated to anosognosia. The role of extrapyramidal movements and specifically dyskinesia and Parkinsonism as prognostic factor in schizophrenia is not well known. In this prospective work the relationship of dyskinesia and other extrapyramidal symptoms with one-year psychiatric outcome was studied in a cohort of 112 patients suffering from First Episode of Schizophrenia Spectrum disorder and treated with Second Generation Antipsychotics. Results showed that, linear regression model of outcome fitted early response (p= 0.001), abuse of alcohol (p= 0.026), higher occupational level reached (p= 0.031), younger age at onset (p= 0.033), dyskinetic movements during the first twenty-four week (p= 0.034) and female sex (p= 0.039), but not first eight weeks Parkinsonism, as significant variables (adjusted R^2 0,416). Direction of the association of dyskinesia with severity of illness was negative. Thirty-two patients showed dyskinesia in the first twenty-four weeks and six patients were diagnosed as Tardive Dyskinesia during the follow-up of the study (5.3% out of 112 patients in the initial sample, 8.3% out of the 72 patients that complete the follow-up. The potential role of early dyskinetic movements as a window of the dopaminergic system in schizophrenia is postulated.

Resum

Molts trastorns del moviment observats en pacients esquizofrènics passen desapercebuts, especialment els de lleu o moderada intensitat o bé els associats amb anosognosia. El valor dels moviments extrapiramidals i específicament de la discinèsia i el parkinsonisme com a factor pronòstic en l'esquizofrènia no és ben conegut. En aquest estudi prospectiu, s'estudia la relació de la discinèsia i altres símptomes extrapiramidals amb l'evolució a un any del trastorn en una cohort de 112 pacients en el seu primer episodi de l'espectre esquizofrènic tractat amb antipsicòtics de segona generació. Els resultats van mostrar que en el model ajustat de regressió lineal, la resposta primerenca al tractament (p = 0.001), l'abús d'alcohol (p = 0.026), el nivell ocupacional més alt aconseguit (p = 0.031), l'edat d'inici més primerenca (p = 0.033), els moviments discinéticos durant les primeres vint i cuatre setmanes (p = 0.034) i el sexe femení (p = 0.039), però no les primeres vuit setmanes de Parkinsonismo, com a variables significatives (R² ajustat 0.416). La direcció de l'associació de les discinèsies amb la severitat de la malatia fou negativa. Trenta-dos pacients van mostrar discinèsia en les primeres vint setmanes i sis pacients van ser diagnosticats com discinèsia tardana durant el seguiment de l'estudi (5.3% de 112 pacients en la mostra inicial, 8.3% dels 72 pacients que van completar el seguiment). Es postula el potencial dels primers moviments discinéticos com una finestra del sistema dopaminèrgic en l'esquizofrènia

Parauless clau: Evolució esquizofrènia, discinesia, antipsicòtics.

Resumen

Muchos trastornos del movimiento observadas en pacientes esquizofrénicos pasan desapercibidas, especialmente las de leve o moderada intensidad o bien las asociadas con anosognosia. El valor de los movimientos extrapiramidales y específicamente de la discinesia y el parkinsonismo como factor pronóstico en la esquizofrenia no es bien conocido. En este estudio prospectivo, se estudia la relación de la discinesia y otros síntomas extrapiramidales con la evolución a un año del trastorno en una cohorte de 112 pacientes en su primer episodio del espectro esquizofrenico tratado con antipsicóticos de segunda generación. Los resultados mostraron que en el modelo ajustado de regresión lineal la respuesta temprana al tratamiento (p = 0.001), el abuso de alcohol (p = 0.026), el nivel ocupacional más alto alcanzado (p = 0.031), la edad de inicio más temprana (p = 0.033) , los movimientos discinéticos durante las primeras veinticuatro semanas (p = 0.034) y el sexo femenino (p = 0.039), pero no las primeras ocho semanas de Parkinsonismo, como variables significativas (R² ajustado 0.416). La dirección de la asociación de les discinèsies con la severidad de la enfermedad fué negativa. Treinta y dos pacientes mostraron discinesia en las primeras veinticuatro semanas y seis pacientes fueron diagnosticados como discinesia tardía durante el seguimiento del estudio (5.3% de 112 pacientes en la muestra inicial, 8.3% de los 72 pacientes que completaron el seguimiento). Se postula el potencial de los primeros movimientos discinéticos como una ventana del sistema dopaminérgico en la esquizofrenia.

Palabras clave: Evolución esquizofrenia, discinesia, antipsicóticos.

INDEX

1   INTRODUCTION

The burden of schizophrenia and other psychotic disorders devastate patients and their family lives with high direct and indirect costs in terms of suffering and lack of productivity (Awad & Voruganti, 2008; Knapp, Mangalore, & Simon, 2004).

1.1   DEFINITION OF SCHIZOPHRENIA

Schizophrenia was described at the end of the XVIII century by Pinel 1798 and shortly afterwards by Haslan 1809 (Wyatt, Alexander, Egan, & Kirch, 1988). Pinel used the term Démence referred to describe psychosis and Morel called Démence précoce to the condition suffered by many deteriorated patients who were ill since adolescence (Kaplan, Sadock, & Grebb, 1994). By the end of the century, Kraepelin called it dementia praecox describing the symptoms seen in patients but stressing the early deterioration in their cognition and daily functioning. Shortly afterwards Eugen Bleuler referred to this condition as schizophrenia as mind seems to be split in terms of feelings, thoughts and behavior and delineated the four primary symptoms or fundamental symptoms of schizophrenia, namely abnormal associations, autistic behavior and thinking, abnormal affect and ambivalence. Earlier, Kahlbaum described the catatonic states characterized by characteristic psychomotor signs such as psychomotor inhibition, vax flexibility, abnormal postures, agitation, negativism, stereotypies and mannerisms.

In the XIX century and early XX century, the neurologist Reynolds and also Jackson and Clerambault, both psychiatrists, introduced the concept of Positive and Negative phenomena. By the term negative they referred to the lack of activity due to a lesion or lack of function, and by the term positive to the compensational overactivity that arises in other structures to counteract such deficit (Berrios, 1985). The differentiation in positive and negative symptoms have been the basis for the classification of schizophrenia in two types, denominated I and II or positive and negative. Positive or type I schizophrenia when symptoms are predominantly productive or in excess from normal mental activity like hallucinations or delusions. Negative or Type II when there is a lack and deficient mental activity, like emotional flattening and restriction or decreased thinking and volitional activity. Brain imaging, and treatment response are

coherent with this two types schizophrenia which made it very interesting in research framework. Compared to Type II, Type I patients tend to have less brain structural abnormalities and show a favorable response to antipsychotics (Crow, 1980). The concept of a Positive and Negative and Mixed subtypes of schizophrenia was then developed by Andreasen (Andreasen & Olsen, 1982) and as coexisting dimensions by Kay (Kay, Opler, & Lindenmayer, 1988).

Currently, diagnosis of Schizophrenia is based on the presence of characteristic symptoms, such as delusions, hallucinations, disorganized speech, behavior or motor catatonic phenomena and affective flattening, alogia, poverty of speech, avolition. In addition to social and occupational dysfunction and an enough time of disorder duration, and the exclusion of other medical and psychiatric conditions.

Five subtypes of the disorder are distinguished in the current versions of the American Diagnostic and Statistical Manual classifications (i.e. DSM-IV and DSM-5). In Paranoid type clinical picture is mainly based in delusions and auditory hallucinations; in Disorganized type prominent features are disorganized speech, behavior or affect; in Catatonic type clinical picture is dominated by motor symptoms, and echolalia or echopraxia; in undifferentiated type there is no predominance of any of the symptoms referred in other subtypes; and in Residual type is reserved to patients to whom clinical presentation is absent of any of the these symptoms but show a have continuing evidence of the disorder. This evidence is shown by attenuated positive symptoms or by negative symptoms, such as avolition, flattening affect, emotional blunting, social withdrawal. (APA 2000)

The International Classification of Diseases (WHO) emphasizes the distortions of thinking and perception in the definition of schizophrenia. Classical phenomena denominated first-rank symptoms by Kurt Schneider are the most characteristical, like thought echo, insertion or withdrawal, thought broadcasting, delusions of control and hallucinatory voices commenting or discussing the patient in the third person (WHO, 1993).

Cognitive symptoms affects all subtypes of schizophrenic patients in a greater or lesser degree (Green et al., 2004; Keefe & Harvey, 2012).

Nowadays Schizophrenia is considered a group of disorders more than a single entity, sharing more or less common clinical characteristics (Carpenter, 2011), but with different etiological, clinical full expression and outcome.

1.2 EPIDEMIOLOGY

Incidence of schizophrenia is considered around 10-20 per 100.000 and year (Messias, Chen, & Eaton, 2007). Prevalence is approximately 0,5-1,5% of the population (Kessler R, McGonagle K, 1994; McGrath et al., 2004), with little variation across countries and cultures (Jablensky et al., 1992). Clinical presentation in different cultures is diverse (Brekke & Barrio, 1997; Thakker & Ward, 1998) due to the importance of beliefs and values in the expression of the disorder. Some differences between urban and rural areas have been detected (Lederbogen et al., 2011; Lewis, David, Andréassson, & Allebeck, 1992).

1.3 ETIOLOGY

The etiology of schizophrenia is considered to be the result of a complex interaction between hereditary-genetic and environmental components (Caspi & Moffitt, 2006; Moffitt, Caspi, & Rutter, 2005; Tienari et al., 2003).

1.3.1 Hereditary factors

Classic hereditary studies of risk in members of affected families showed that first-degree relatives develop schizophrenia in about ten percent; and the risk becomes lower as degree of kinship is less (K S Kendler & Gardner, 1997; Kenneth S. Kendler et al., 1993). Actually, there is a strong familial aggregation of schizophrenia and schizophrenia spectrum disorders in biological families of patients with odds ratios varying from 16 in schizophrenia to 4 in other non-affective psychosis. These results have been replicated in three independent family studies, the Danish Adoption Study, the Iowa 500non-500 family study, and the Roscommon family study (K S Kendler & Gardner, 1997; Kety, Rosenthal, Wender, & Schulsinger, 1971). Adoptive families contribute to occurrence of schizophrenia only in those subjects at high genetic risk families (Tienari, P., Wynne, L.C., Sorri, A., 2004).

Some genes have been postulated as susceptibility genes for Schizophrenia causation in different degree: COMT, DTNBP1, NRG1, RGS4, GRM3, DISC1, GT7, DAA0, PP3CC, CHRNA7PRODH2, AKT1. They are in different locations within the cromosomes 22,6,8,1,7,13,12,15,14 (Jones & Buckley, 2006), specially 6p and 8p, encoding diverse proteins and affecting different functional clues (Wildenauer et al., 1996). Some are related to the dopamine metabolism (i.e. COMT) while others are associated to other neurotransmitters like serotonine and glutamate or intervene in more general physiologic processes, such as cellular calcium cascades or in immune response (Ripke et al., 2014).

Then, Schizophrenia is currently considered to be a highly polygenic disorder with a complex array of contributing risk loci across the allelic spectrum. Its specifity for schizophrenia is low as other psychiatric illnesses share the same risk genes and alleles, specially, bipolar disorder, intellectual disability, major depressive disorder and autism spectrum disorders (Kavanagh, Tansey, O'Donovan, & Owen, 2015). Genetic contribution is also is considered independent of sex (S. H. Lee et al., 2012)

On the other hand, phenotypic expression of the disorders is due to complex interactions between risk alleles and environmental risk factors. For instance, gene-enviroment pathogenetic interactions in the transition to psychosis have identified the importance of serotonin neurotransmission together with environmental stress factors (Bernardo 2017)

1.3.2   Enviromental factors

Many and diverse environmental factors of risk in schizophrenia have been identified. From prenatal and perinatal to later stressors interfering in the neurodevelopment, such as old parental age, CNS infections pre-birth and during childhood (Cannon et al., 2002; Poulton et al., 2000; Rapoport, Giedd, & Gogtay, 2012), pregnancy and birth complications, season of birth, brain damage and under nutrition; and later stressors such as, cannabis and drug use (Arseneault, Cannon, Witton, & Murray, 2004) and stressors as a result of social isolation and stress like ethnicity and density of peers (Selten & Cantor-Graae, 2007), or other factors: traumatic and violence antecedents (McGowan, PO; Sasaki, A; D'Alessio, AC; Dymov, S; Labonté, B;

Szyf, 2009) and urbanicity (Lederbogen et al., 2011; Peen, Schoevers, Beekman, & Dekker, 2010).

It has been proposed a model of diathesis-stress in which biological and environmental factors are synergistic in the susceptibility or the resilience to psychosis with a temporal sensitivity linked to critical developmental periods (Walder, Faraone, Glatt, Tsuang, & Seidman, 2014). This model updates the classic diathesis-stress model by Zubin (Zubin & Spring, 1977) or vulnerability-stress model by (Nuechterlein et al., 1994).

The common age of conversion or onset of schizophrenia is adolescence and early youth. This time period is considered of high risk for schizophrenia. While early postnatal period is characterized by neurogenesis and massive dendritic connectivity, the adolescent period is characterized by also crucial neurodevelopmental events such as dopamine dependent prefrontal innervation (Weinberger, 1987), synaptic pruning and the final maturation of the NMDA and GABA-glutamate dependent prefrontal cortex circuits (Bale et al., 2010).

Genes and environmental factors may sensitize the dopamine system increasing vulnerability to acute stress. In current dopaminergic hypothesis of schizophrenia includes the increase of striatal dopamine synthesis and release in response to psychosocial stress, linking dopamine neurotransmision to the onset of schizophrenia (Howes, Mccutcheon, Owen, Murray, & Studies, 2017), consistently with the diathesis-stress model.

1.4   BIOLOGICAL MARKERS OF RISK IN SCHIZOPHRENIA

Many putative biomarkers from different fields have been studied: CNS structural and functional, neurophysiological (mismatch negativity MMN, P300 and P50 ERP, prepulse inhibition (PPI), neural synchrony alterations), sleep abnormalities, neurochemical (N-acetyl-aspartate reductions, membrane phospholipids, dopamine, Glutamate, GABA neurotransmitters), and neuropathological (reduction of brain weight, asymmetry cortical and limbic brain regions cell disorganization) (Fusar-Poli et al., 2007; Keshavan, Tandon, Boutros, & Nasrallah, 2008).

More recently, under the dopaminergic theory of schizophrenia, dopamine-related disruption of striatal-cortical connectivity linked to dopamine overactivity have been demonstrated (Horga et al., 2016; Howes et al., 2012), may be due to increased presynaptic synthesis of dopamine (Fusar-Poli & Meyer-Lindenberg, 2013), which is associated with worsening of psychotic symptoms in amphetamine challenges of dopamine release (Abi-Dargham et al., 1998; Laruelle, Abi-Dargham, Gil, Kegeles, & Innis, 1999), and dopaminergic hyperactivity in the nigrostriatal pathway (Winton-Brown, Fusar-Poli, Ungless, & Howes, 2014). These evidences point to a dysregulation of the dopamine system.

Nevertheless, no single biomarker has been found for schizophrenia. Actually, when the heterogeneity associated with schizophrenia is taken into account it results in the need of multiple biomarkers that identify the multiple underlying pathophysiological processes involved in this condition (Weickert, Weickert, Pillai, & Buckley, 2013).

1.5 THE NATURAL COURSE OF SCHIZOPHRENIA

Typically, the clinical manifestations of schizophrenia begin in late adolescence or youth as an acute episode. So, the age of onset is typically at young ages with different proportions of positive phenomena, like delusions and hallucinations, negative symptoms like social withdrawal and blunted affect and cognitive symptoms.

In some cases, illness seems to be related to abnormal neurodevelopmental processes that started years before the illness onset (Rapoport et al., 2012); while in others, conversion is more abrupt in subjects who showed a normal development.

However, in many cases the onset of psychosis is preceded by a variable period of non-specific phenomena or prodromes. In this prodromal phase, patients show social withdrawal, impairment in their general functioning and motivation, odd behaviors, odd ideation and behavior, feelings and perceptual experiences, change in habits, along with emotional distancement or inappropriateness (Fusar-Poli et al., 2013; Tandon, Nasrallah, & Keshavan, 2009).

In the transition to psychosis of subjects at high-risk some clinical factors have been identified in both, the North American Prodrome Longitudinal Study (NAPLS) (Seidman et al., 2010; Thompson, Nelson, & Yung, 2011) and the European Prediction of

Psychosis Study (EPPS) (Rurhmann et al., 2010). They reported that genetic risk with functional decline, high unusual thought content and low social functioning, in addition to history of substance abuse are associated to the risk of transition.

The incipient disorder use to appear as clinical precursor with prodromal subthreshold clinical symptoms (P. McGorry, 2011). Then, the first three to five years after the schizophrenic onset are considered of crucial interest or "critical period" as they can be predictive and of great value in the conformation of the subsequent course (De Girolamo, Dagani, Purcell, Cocchi, & McGorry, 2012). As short-term outcome is associated to medium-term outcome, and medium-term is associated to long-term outcome (Harrison et al., 2001), it becomes very important to get the best treatment strategy early in order to facilitate better outcomes.

The course of schizophrenic disorders can be either continuous, or episodic with progressive or stable deficit, or there can be one or more episodes with complete or incomplete remission (WHO, 1993). Most patients suffer episodes of relapse followed by symptom remission during years while others show sustained impairment and disability with poor functioning (Wiersma, Nienhuis, Slooff, & Giel, 1998). Around ten percent of patients remain severely ill over long periods of time (Jablensky 1992; Gerbaldo 1995).

In the long-term, half of the patients suffer a minimal impairment after few episodes, other patients are increasingly impaired in their functioning and suffer several episodes (Harding, Zubin, & Strauss, 1992; Shepherd, Watt, Falloon, & Smeeton, 1989). But, variability in course and outcome is high, again due to the interaction of hereditary and environmental factors both protective and risk factors (Nuechterlein et al., 1994).

A study of symptom remission and recovery in patients with less than two years length of illness showed that only one percent recovered, seven percent with good functional outcome and 22 % had symptom remission over one year after the acute episode (Ventura et al., 2011). Therefore, outcome is considered bad. However, there is some controversy on whether a diagnosis of schizophrenia is possible when full and durable remission is installed without new episodes over the years and decades. For

some, it is and actually happens in as much as 15% of first-episode patients (P. D. McGorry, 2002).

Relapses have been associated to a kind of neurotoxic effect produced by the own psychotic state; but at the same time, early non-response seems to facilitate non-adherence to treatment and then add risk of relapse, (Remington et al., 2014). Up to four episodes, every new relapse adds 17% of chance of non-remission (Wiersma et al., 1998). After repetitive relapses, a decline in the treatment response have been observed. These studies indicates a progressive refractoriness as number of episodes increase (J. A. Lieberman et al., 1996).

In addition, one third of the patients show suicide behaviors (Allebeck 1987) and 5-10% of them commit suicide (Palmer, Pankratz, & Bostwick, 2005; Tsuang, 1978) especially during initial phases and after first episodes, probably because the catastrophic feelings, depressive symptoms and lack of coping skills (Hamera, Peterson, Young, & Schaumloffel, 1992; Koreen et al., 1993) and support system, especially in patients who showed abrupt onset and delayed treatment (Wiersma et al., 1998).

Schizophrenic patients die prematurely not only because of suicidal behaviors but also due to somatic conditions which make mortality and morbidity higher than in the general population (Melle et al., 2006; Zhuo, Tao, Jiang, Lin, & Shao, 2017). Life expectancy is twenty per cent shorter and mortality is increased two-three times in patients (Brown, Kim, Mitchell, & Inskip, 2010). Cardiovascular morbidity in schizophrenia due to life habits, social deprivation, antipsychotic prescription and reports of heavy alcohol use, is an urgent problem of public health (Osborn 2015, Correll 2017). In spite of health contacts patients are undiagnosed and die twelve to fifteen years earlier than the general population (Crump, Winkleby, Sundquist, & Sundquist, 2013; Oakley et al., 2018).

1.6 OUTCOME PRONOSTIC FACTORS

Outcome showed by patients is very diverse being difficult to make a reliable prediction of the outcome from the first episode of illness in the individual patient (Shitij Kapur, 2011). Classically, sociodemographic factors like younger age, male sex

and lower premorbid adjustment have been associated to worst outcome. Clinical factors such as type and characteristics of onset (rapid onset with better outcome), baseline severity, comorbidities such as substance-use disorders, DUP, lack of adherence to treatment, delayed response to treatment (Carbon & Correll, 2014) and biological factors like structural imaging, platelet MAO activity, or prolactin level change after antipsychotic treatment initiation, have been associated to functional outcomes (Levine, Rabinowitz, Uher, & Kapur, 2015; J. A. Lieberman et al., 1996).

1.6.1 Age and Sex

Sex and age seems to be relevant variables in the prognosis of schizophrenia outcome and course. Compared to men, women tend to show later age at onset, more favorable course and better functioning. In addition, later age of onset is associated with more chances to the development of educational, occupational and social skills. Later onset cushions damage and enhances recovery (Hafner et al., 1998) due to the fact that more achievements in education, occupation and affective life have been already accomplished. But, in post-menopausal women outcome is worst compared to men (Hafner et al., 1998).

1.6.2 Premorbid Adjustment

A relationship of premorbid adjustment and outcome has been consistently replicated (Alvarez et al., 1987; Meng et al., 2006). In a multicenter study of the relationship between premorbid characteristics and treatment response in patients with recent-onset psychosis conducted in eleven countries (n=534), (Rabinowitz, Harvey, Eerdekens, & Davidson, 2006) a clear association of good premorbid functioning and better response to treatment was found. When treatment adherence is good, then premorbid adjustment is probably the most replicated variable associated to outcome.

1.6.3 Duration of untreated illness

Duration of untreated psychosis (DUP) is usually long. A mean time of 30 to 114 weeks from onset of psychotic symptoms to initiation of antipsychotic treatment has been reported (Birchwood, 1992; Larsen, McGlashan, Johannessen, & Vlbe-Hansen, 1996). A meta-analysis of DUP showed a positive association with severity whilst less

DUP was associated with better response to treatment in all clinical areas (Perkins, Gu, Boteva, & Lieberman, 2005). This is consistent with the theory of a toxic effect produced by the illness which would impair outcome of treatment, but is critically reviewed (Rund, 2014). The expected cognitive impairment as a result of untreated illness is not confirmed (Goldberg et al., 2009) and the strength of the association with outcome result only moderate (Marshall et al., 2005).

1.6.4 Comorbid Substance Abuse

Schizophrenic patients are a highly vulnerable population to substance abuse. Prevalence rates from the literature vary from 3% to 47% for drugs and alcohol (Larsen et al., 2006). Overall, drug and alcohol abuse are highly prevalent in contemporary first-episode psychosis samples with similar patterns to the general population. It is considered that risk of cannabis abuse is increased by five and cocaine abuse by thirteen (Regier et al., 1990). Drug-abuse in Schizophrenia is associated to male gender, younger age, better premorbid social and poor premorbid academic functioning (Buckley, Miller, Lehrer, & Castle, 2009; Larsen et al., 2006).

Attempts to improve negative symptoms is considered one of the main reasons to explain such a high risk of substance abuse. By the activation of reward dopaminergic circuits, the patient seeks to overcome illness and the eventual antipsychotic treatment side-effects (Volkow & Morales, 2015). At the same time a deficient control of behavior in schizophrenia can extent substance seeking behavior.

Not only substance abuse have direct effects in the psychosis course, comorbidity of subtance abuse also enhances the risk of extrapyramidal symptoms (EPS) during antipsychotic treatment (Carrà et al., 2016), which in turn also facilitate non-adherence to treatment.

1.6.5 Treatment Adherence

Lack of antipsychotic treatment increases risk of relapse by two to six times (Leucht et al., 2012). Then, adherence to treatment is one of the main factors associated to outcome. Although frequently is not easy to assess, adherence is usually poorer than expected with estimates ranges from 24 to 90% in psychotic patients and is usually considered around 50% of the patients (García-Ribera & Bulbena, 2011).

Adherence is multidetermined by a number of variables ranging from the patient sociodemographic characteristics to factors related to patient/psychiatrist interaction, drug tolerability and organization of care. It is highly associated to lack of insight, tolerability, subjective well-being and movement adverse effects of antipsychotics (García-Ribera & Bulbena, 2011). Akathisia and neuroleptic-induced dysphoria seem to mediate at least part of the lack of adherence to antipsychotic treatment (Van Putten, May, & Marder, 1984) and more recently, a direct relationship of dysphoria to high DA blockade has been shown (De Haan et al., 2003; Mizrahi et al., 2007; Voruganti & Awad, 2006). Use of long-acting injectables (LAI) or depot medications from early phases seem to improve outcome (Parellada, Velligan, Emsley, & Kissling, 2012), but treatment guidelines limit the use of LAI to multiple-episode patients and to openly nonadherent patients (John M. Kane & Garcia-Ribera, 2009).

1.6.6 Early response

Early improvement at two to six weeks of treatment initiation seems to be a good predictor of later response and outcome (Derks, Fleischhacker, Boter, Peuskens, & Kahn, 2010; Leucht & Zhao, 2014; Samara et al., 2015), not only based on the psychopathology scale ratings but also on the basis of the patient own early perception. Patient's perception at week two can successfully predict response or not at week eight (Ascher-Svanum et al., 2014).

A review of the clinical predictors of non-response to antipsychotics in schizophrenia (Carbon & Correll, 2014) shows that most of the predictors are actually non-modifiable (male sex, younger age at onset, poor premorbid adjustment). Nevertheless, they can help in the tailoring of the therapeutic approach, advancing strategies of refractoriness to improve the chances of better outcomes. Treatment has to be planned not only in relation to current or past severity and clinical characteristics, but also in terms of the prognostic factors associated. When adequate treatment is provided in addition to rehabilitation programs during the early course of schizophrenia (or "window of opportunity"), recovery in a significant proportion of patients does happen (Harrison et al., 2001; Wiersma et al., 1998).

1.7   PHARMACOTHERAPY OF SCHIZOPHRENIA

<u>From Chlorpromazine to the third generation of antipsychotics</u>

Modern pharmacologic treatment of schizophrenia has replaced former biological treatments based in the induction of Insulin coma, chemical seizures, lobotomies and electroconvulsive therapy in non-anesthetized patients. Antipsychotic drug treatment represents the first-line effective and specific treatment for psychosis. Their efficacy has been demonstrated not only in the treatment of the acute phase of schizophrenia, but also in the prevention of relapse (Leucht et al., 2012). For most patients, the antipsychotic drug treatment must be continued indefinitely.

It is considered that introduction of antipsychotics drugs greatly facilitated the externalization of a considerable portion of patients from psychiatric hospitals, allowing their reinsertion into the community and improving their quality of life.

1.7.1   First Generation Antipsychotics

In the fifties, french psychiatrists Delay and Deniker tested chlorpromazine in a group of schizophrenic patients with different doses observing for first time a quite different effect from the sedative effect seen with other drugs. A specific effect on the delusions and hallucinations was observed without relevant sedation (Carles Garcia-Ribera & Ruiz Ripoll, 2010). The antipsychotic effect that appeared after several days or weeks was preceded by an involuntary effect, eminently motor and emotional, as of "neuronal stiffening", characterized by "psychomotor retardation, emotional stillness and affective indifference", which gave rise to the term neuroleptic or conventional antipsychotic, later renamed First Generation Antipsychotics (FGA). Subsequently, multiple compounds have been developed with very diverse antagonistic DA2 receptor potencies and, therefore, range of effective doses. The main FGA of reference and first being sintetyzed is chlorpromazine. Shortly after, a diversity of phenothiazine, piperidine compounds, butyrophenones, thioxanthenes and benzamides were synthetized.

FGA have many limitations: Twenty to forty percent of patients do not obtain an adequate response to treatment and approximately 35% of treated patients relapse every year. Although they are effective for positive symptoms they are not effective

against or even worsen negative symptoms. In addition, they produce a high incidence of extrapyramidal movement abnormalities and sexual effects, among a wide variety of adverse effects. Although it is rare, they can induce potentially deadly neuroleptic malignant syndrome. These limitations served to catalyze the investigation of new antipsychotics with an "atypical" effect.

So far, the common mechanism of action of all the antipsychotic drugs with demonstrated clinically utility are dopamine antagonists. This is one of the fundamentals of the dopaminergic hypothesis of schizophrenia (Howes & Kapur, 2009). Dopamine antagonism at D2 receptor family has been shown to be correlated with effective clinical dose of the different antipsychotic compounds (P. Seeman & Lee, 1975). Moreover, results from PET scan studies show that there is a magnitude of D2 receptor occupation needed to get an antipsychotic effect and that is around 60 %. while the occupation needed to induce extrapyramidal motor effects is around 75-80% (Farde et al., 1992; S Kapur, Zipursky, Jones, Remington, & Houle, 2000; Nordström et al., 1993). It makes easy to understand why both effects are commonly linked in FGA treatment which fail to show a clinical dissociation of antipsychotic and extrapyramidal dose.

1.7.2   Second Generation Antipsychtics

By 1960, shortly after the introduction of chlorpromazine in therapeutics, clozapine was synthesized. However, it was devoid of extrapyramidal adverse effects. At that time these were considered a requirement and indicator of real antipsychotic effect. Nowadays, demonstration of the superiority in efficacy and lack of movement disorder induction (J. Kane, Honigfeld, Singer, & Meltzer, 1988) has placed clozapine as the atypical antipsychotic drug of reference. Subsequently, so-called atypical or Second Generation Antipsychotics (SGA) have appeared on the market, as medications lacking of extrapyramidal effects. Risperidone, Olanzapine, Ziprasidone, Amisulpride, Quetiapine, belong to this group of antipsychotic drugs. SGA show a dissociation in the doses needed to obtain clinical response and those needed to induce extrapyramidal motor effects (Jibson & Tandon, 1998). This allows an effective antipsychotic treatment at doses still far enough from those inducing extrapyramidal effects (S. Kapur & Seeman, 2001).

Mirroring the superiority of clozapine other criteria of atypicality includes efficacy in disorders resistant to FGA treatment, effect on the negative symptoms of schizophrenia, lack of elevation of prolactin levels and lack of risk of tardive dyskinesia. (Carles Garcia-Ribera & Ruiz Ripoll, 2010).

The SGA are very different substances both in their chemical structure and in their activity on the receptors. Most, like Risperidone and Ziprasidone are mixed D2 and serotonin 5HT2 antagonists, with strong serotonin 5HT2 potency. Others show a broad spectrum of activity on various neurotransmission systems: Clozapine, Olanzapine, Quetiapine; or are selective on the dopaminergic receptor: Sulpiride, Amisulpride. Finally, newer generation of antipsychotic drugs are partial agonists at D2 receptor (and are also called Third Generation Antipsychotics): Aripiprazol, Bexpriprazole (Stępnicki, Kondej, & Kaczor, 2018).

The dopaminergic neurons are distributed in localized areas of the CNS, giving rise to the following pathways: tuberoinfundibular, responsible for the endocrine effects of antipsychotics; mesocortical, responsible for a large part of the neuroleptic effects of the antipsychotics and anatomical substrate of akathisia; nigrostriatal, responsible for extrapyramidal effects; mesolimbic pathway, responsible for the antipsychotic effect, especially on the positive symptomatology.

Several hypotheses related to the atypicality of SGA have been formulated (Carles Garcia-Ribera & Ruiz Ripoll, 2010): the regional selectivity of the dopaminergic antagonism, and its preferential activity on the mesolimbic dopaminergic neurons over nigrostriatal dopaminergic pathways (Palacios & Mengod, 1996); the selectivity for the D4 or D3 receptor; the combined blockade D2-5HT2; a wide spectrum of receptor blockade; the low affinity for the D2 receptor and an adequate D1 / D2 affinity ratio and the fast dissociation of the antipsychotic drug from the DA receptor.

Both the D3 (Sokoloff, Giros, Martres, Bouthenet, & Schwartz, 1990) and D4 receptors show a preferential distribution over the limbic structures. This fact, together with the high affinity of clozapine for the D4 receptor (Van Tol et al., 1991) (also called "clozapine receptor") makes them particularly interesting as a substrate for the "atipicity" of some SGA.

The combined blockade D2-5HT2: blockade of 5HT2a receptors seems to release the inhibition on the nigrostriatal dopaminergic activity exerted by the dopamine antagonists (Herbert Y. Meltzer & Huang, 2008). In the clinic, serotonergic blockade reduces extrapyramidal effects caused by dopamine antagonists. In addition, for some authors the controversial effect on the negative symptomatology may have its basis of action in this combined blockade. With the exception of selective antagonists, all new generation antipsychotics in addition to clozapine exhibit 5HT2 antagonist activity (Kuroki, Nagao, & Nakahara, 2008; H. Y. Meltzer & Massey, 2011).

A wide spectrum of receptor blockade: Failure to find a single pharmacodynamic effect that explains the superiority of clozapine in its clinical characteristics has led some lines of research towards the design of drugs reproducing the complex and peculiar profile of receptor activity of this substance, without the hematological risk of its clinical use (Gerlach & Garcia Ribera, 1996).

The low affinity for the D2 receptor and an adequate D1 / D2 affinity ratio seems to improve the clinical profile of the D2 antagonists in terms of efficacy against negative symptoms or the risk of inducing extrapyramidal effects (Ahlenius, 1999), perhaps making less necessary a high D2 blockade to obtain the antipsychotic effect or a D1 receptor agonism.

Finally, the fast dissociation of the antipsychotic drug from the DA receptor facilitate the action of endogenous dopamine and avoid the appearance of pseudo-negative symptoms and adverse effect (S. Kapur & Seeman, 2001).

1.7.3 Adverse Effects

Many kinds of adverse effects affecting the whole economy with an extensive range of incidence are possible during treatment. Most epidemiologically important are neurological mainly extrapyramidal and metabolic adverse effects whilst very few are life-threatening like hematologic severe dyscrasias and neuroleptic malignant syndrome (Carles Garcia-Ribera & Ruiz Ripoll, 2010). The potential effect of the antipsychotic treatment contributing to the overall excess in mortality has been recently ruled-out (Schneider-Thoma et al., 2018).

Schizophrenia has been associated to many of neurological signs including motor coordination, sensory integration, sequencing of complex motor acts, spontaneous motor activity, gestures and involuntary movements; extrapyramidal signs like tremor, rigidity, dystonia and dyskinesia are also seen during the examination in schizophrenia. Extrapyramidal movement disorders appear in classic descriptions of schizophrenic patients earlier than antipsychotic drugs were used. With the introduction of antipsychotic treatment these movements appear more frequently and sometimes in severe and acute forms. Then, antipsychotic drugs and the own psychiatric illness are potentially associated to the risk of producing extrapyramidal signs. However, movement disorders in treated patients are attributed in a biased way almost exclusively to the antipsychotic treatment.

The classification of extrapyramidal disorders seen in schizophrenic patients under antipsychotic treatment follow the said framework and considered drug induced. All antipsychotic drugs can induce extrapyramidal symptoms to a greater or lesser degree. Induced extrapyramidal symptoms are classified depending on the time lapse after the drug administration: short and long term.

1.8.1   Short-term induced extrapyramidal symptoms

Acute Dystonia appears acutely, hours or even minutes after the first administrations of the drug or increase of dose in the form of hypertonic postures especially in the oral and cervical region. It has involuntary character, produces pain and anxiety. It occurs more frequently with the more potent neuroleptics in their dopamine antagonist effect.

Antipsychotics can also induce a full Parkinsonism syndrome characterized by the presence of akinesia or hypokinesia, rigidity and rest tremor. Cogwheel phenomena can be observed in the extremities by passive mobilization. It appears sub-acutely in the first two to four weeks of treatment.

Both Acute Dystonia and Parkinsonism are due to the antidopaminergic effect of the antipsychotics, which causes an imbalance between the dopaminergic and cholinergic systems in the basal ganglia (Ward & Citrome, 2018). The efficacy of the

administration of anticholinergic drugs or reduction of the antipsychotic dose is consistent with this physiopathological mechanism. After ten or fourteen weeks of treatment there is often a phenomenon of tolerance that makes treatment of parkinsonism unnecessary.

Akathisia is a phenomenon of uneasiness and restlessness, which, leads to secondary motor hyperactivity. It is perceived as an urge to move which is felt as exogenous, when the cognitive situation of the patient allows it. Sometimes it should be distinguished from the anxiety. Onset is usually subacute in days or first weeks of treatment. Its appearance has been related to dopaminergic antagonism of antipsychotics at the mesocortical dopaminergic pathway. Antipsychotic switch or beta2-blockers medication are the most effective treatment.

Hyperkinetic movements like dyskinesia were reported in relation to other short-term motor syndromes after introduction of FGA, by Delay and Deniker in the sixties (Deniker 1969, Gerlach 1979). This movements are repetitive and involuntary, typically appearing in oro-facial structures. Some Dyskinesias appear early in the course of treatment with antipsychotics and anticholinergic treatment improve it. They result from the initial dopamine hypoactivity, also manifested as Parkinsonism and is not a prerequisite for later development Tardive Dyskinesia (Gerlach 1979). During the last decades, several terms have been introduced in the literature to refer to the same clinical feature: Hyperkinesia, Emergent Dyskinesia, Spontaneous Dyskinesia, Schizophrenic Dyskinesia, Initial Hyperkinesia, Tardive-like Dyskinesia or simply Dyskinesia. There are not universal definitions for the terms in use, confusing the comparison of the results of studies.

There are not consensus on the definition and criteria for diagnosis of dyskinetic movements, apart from Schooler and Kane Research Criteria (SKRC) for Tardive Dyskinesia (N. R. Schooler & Kane, 1982)(see annex 6). When dyskinetic movements does not fulfill SKRC other terms are used: Spontaneous Dyskinesia, Emergent Dyskinesia and Tardive-like Dyskinesia.

1.8.2   Long-term induced Extrapyramidal symptoms

Tardive Dyskinesia is archetype of long-term motor disorder induced by antipsychotics. It is classically defined as an involuntary hyperkinesia that appears after long periods of antipsychotic treatment. In its most frequent manifestation repetitive movements of lingual and labial protrusion, suction and chewing are observed. It is characteristic the anosognosia of movements at early stages. Anticholinergic treatment increases the severity of movements and dopamine antagonists relieve them. Tardive Dyskinesia is considered the clinical manifestation of a dopamine hyperactivity because of hypersensitivity or up-regulation of dopaminergic pathways after a prolonged treatment with antipsychotics. Additional mechanisms, especially GABA neurotransmission are involved.

Tardive Dyskinesia (TD) has been a major concern during treatment with First Generation Antipsychotics (FGA). Epidemiological studies reported a cumulative incidence rate of 5% of TD per year during the first five years of treatment. The overall prevalence of 23.5%, ranging 16 to 43% (Daniel Tarsy & Baldessarini, 2006), although is lower in outpatients (12.3%) (J M Kane, Woerner, & Lieberman, 1988). In longitudinal studies of First Episode Schizophrenia (FES), carried out in FGA-treated patients, Chakos et al. reported an incidence rate of persistent TD in a group of FES patients treated with FGA fluphenazine of 4,8% in the first year and 2,4% in the second year of treatment (Chakos et al., 1996); Oosthiuzen et al (2003) studied FES patients treated with low dose of FGA Haloperidol (mean 1.68 mg per day) during twelve months and they found that 7 out of 57 (12.28%) subjects developed TD according to SKRC (Schooler and Kane 1982) (Oosthuizen, Emsley, Maritz, Turner, & Keyter, 2003). There is an important heterogeneity of the samples studied which could explain the variability of the results reported (Owens, 2014).

The lower rate of Extrapyramidal Symptoms (EPS) associated to Second Generation Antipsychotics (SGA) has alleviated the concern about TD (Lohr, 2005). In the first studies with SGA, some authors reported an incidence rate of TD of only 0,52% in patients treated with Olanzapine, compared to 7,45% in the Haloperidol treated group (Glazer, 2000). It has been noted an increase in reported incidence of TD in

schizophrenic patients treated with SGA (Correll & Schenk, 2008; Woods et al., 2010; Zhang et al., 2013).

In a systematic review of incidence of TD across 12 studies and more than 28,000 patients from Correll and Schenk (2008) was 3.9 % per year, compared to 5.5% of FGA-treated patients. Incidence of TD from Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study comparing different SGA with FGA perphenazine, showed from 0,7 to 2,2% in SGA and 2,7% in perphenazine group(Miller et al., 2008). Secondary analyses from Cost Utility of the Latest Antipsychotics in Schizophrenia Study Band-1 (CUtLASS-1) showed 8% TD rate at 52 weeks in both SGA and FGA groups of treatment (Peluso, Lewis, Barnes, & Jones, 2012). In one study involving FES adults (mean follow-up: 206 days), 1.8% treated with risperidone and 3.3% in the haloperidol group showed persistent TD according to SKRC for Tardive Dyskinesia (N. Schooler et al., 2005).

Studies of incidence show different results depending on case definition (use of research criteria), type of SGA (wide spectrum or D2/5HT2 receptor antagonists), psychiatric diagnosis, age of patients, and methodology. Most studies are focused in older subjects or patients formerly treated with FGA, making difficult to draw conclusions applicable to get reliable data on the risk of TD associated with SGA use in naïve patients. In other studies, Dyskinesia is often used as safety end-point of clinical trials and is based on spontaneous reports and neither rigorously assessed nor defined (John M. Kane, 2004).

Like in studies of incidence, rates of prevalence under SGA treatment also varies considerably. In the meta-analysis published in 2017 by Carbon et al involving 41 studies and 11,493 patients, rates were lower with current SGA (20.7%) vs current FGA treatment (30.0%). Particularly low TD prevalence (7.2%) was found in the treatment of FGA-naive subjects relative to SGA-treated cohorts with likely prior FGA exposure (23.4%) (Carbon, Hsieh, Kane, & Correll, 2017).

Although it is generally believed that SGA reduce the risk of TD versus FGA, there have emerged concerns that SGA treatment may only delay the onset of TD (Kane 2004) but not eliminate the risk of Tardive Dyskinesia.

1.8.3 Extrapyramidal disorders in drug naïs patients

The study of movement disorders in schizophrenia has been confounded and misleaded due to the widespread use of neuroleptics (Cassady, Adami, Moran, Kunkel, & Thaker, 1998). Use of antipsychotic drugs is a considerable limitation in the study of movement disorders in schizophrenia as they can induce movement disorders by their selves confounding those spontaneously appeared during psychiatric disorder. In a study of risk factors to develop Tardive Dyskinesia in a psychiatric inpatient population (N= 291), logistic model showed an association of dyskinesia to age and schizophrenia but not to antipsychotic treatment, and raised a possible association between of dyskinesia and schizophrenia; in this study seven out of thirty-two (21.9%) patients without antipsychotic exposure showed dyskinesia (Carlos Garcia-Ribera, Ruiz Ripoll, & Vidal Guitart, 1991). In fact, Kane reported a prevalence of spontaneous dyskinesia in psychiatric patients of about 5% (J M Kane, Woerner, Borenstein, Wegner, & Lieberman, 1986). Therefore, drug naïve population is the framework of preference to get valid evidences. In naïve schizophrenic approximately one third of the patients exhibited parkinsonism (tremor, rigidity or bradykinesia) in contrast to only a 4% rigidity in normal control group, but sample was only twenty-four patients (Caligiuri, Lohr, & Jeste, 1993).

Chatterjee et al studied the prevalence of extrapyramidal signs and dyskinesia in first episode patients. Seventeen percent showed extrapyramidal signs and one dyskinesia (Chatterjee et al., 1995). Rate of spontaneous dyskinesia in first-episode schizophrenia was 10.2%. They had significantly fewer years of education being similar mean age. It is suggested a complex association of vulnerability to psychosis and extrapyramidal system that may antedate the onset of the full clinical picture (Gervin et al., 1998).

Puri et al. compared the rates of movement abnormalities in a prospective study of a sample of drug-naive vs neuroleptic treated FES patients (West London prospective study). Results showed that "movement disorder particularly orofacial dyskinesia seems to be part of the clinical presentation of schizophrenia, suggesting that it may be intrinsic to the pathophysiology of schizophrenia". Analysis of baseline data from a trial comparing haloperidol with risperidone in first episode schizophrenia spectrum

(n= 535) showed that twenty eight percent in the non-exposed and 46% in the exposed group showed at least one mild sign of extrapyramidal disorder suggesting overall basal ganglia dysfunction (Honer, Kopala, & Rabinowitz, 2005). Mc Creadie et al studied a sample of 143 schizophrenic naïve patients in India. Dyskinesia was present in 35% and parkinsonism in 15%. In 11 patients both disorders coexisted. They concluded dyskinesia and parkinsonism are integral part of schizophrenia disease process. Co-existence of Parkinsonim and Dyskinesia was considered contradictory due to the opposite state of dopaminergic activity implicit in these disorders, that is hypofunction and hyperfunction simultaneously in the same patient, but it occurs not exceptionally even without antipsychotic exposure (McCreadie, Srinivasan, Padmavati, & Thara, 2005); and pathophysiological explanations are available (Carlos Garcia-Ribera, 1986) . Presence of extrapyramidal symptoms are not rare in naïve schizophrenic patients and the meaning of them remains to be studied.

1.8.4 Recognition and attribution of Extrapyramidal disorders during antipsychotic treatment

Since the marketing of antipsychotic drugs, the movement abnormalities appeared during treatment are normally considered more an accident than an informative factor of the disorder itself. Potential informative value about movement disorder has been neglected. Fenton also complained about the lack of systematic assessment of movement disorders which limited future studies (Fenton, Wyatt, & McGlashan, 1994). The so-called neuroleptic threshold was considered indicative of the effective antipsychotic dose, in the neuroleptic or first generation antipsychotic era. But, other potential informative value of EPS has been neglected or denied in current practice.

Weiden et al conducted a naturalistic study in 1987 about the detection of EPS during the course of inpatient treatment comparing standard care with trained personnel ratings. Staff was blind to the purpose of the study as research personnel were to the medication status and clinical diagnosis as a source of potential bias. Results showed a clear under recognition of EPS (40% to more than 75%), specially dyskinesia and milder forms of akathisia (Weiden, Mann, Haas, Mattson, & Frances, 1987). These results are concordant with those from other studies (Hansen, Glazer, &

Moore, 1986), showing that under recognition happen especially in not yet treated patients (Lauterbach et al., 2001).

1.9 ASSOCIATION OF MOVEMENT DISORDERS WITH PSYCHIATRIC OUTCOME

1.9.1 Studies in psychotic patients

An association of diverse movement disorders and outcome has been reported in the literature. Owens et al (1982) raised a possible relationship between abnormal movements and severe schizophrenia in a sample of 411 chronic schizophrenic inpatients (Owens, Johnstone, & Frith, 1982). Improvement from acute exacerbation was negatively associated to the presence of akathisia, lifetime hospitalization and duration of illness in a sample of 53 patients (Levinson et al., 1990). They suggested that in the group of non-responders fluphenazine dose is not relevant and that akathisia could be a predictor of non-response.

Patients who showed non-response to their antipsychotic treatment have also been studied in the search for early indicators. In the Treatment of Neuroleptic Non-response Schizophrenic Study (Kinon, Kane, Johns, et al., 1993; Kinon, Kane, Chakos, & Munne, 1993) patients (n=115) non-responding at fourth week showed significantly greater acute EPS.

Summarizing, there is cumulative data suggesting an association of extrapyramidal movement disorders and outcome in schizophrenia. What is the specificity of the different EPS, if any remains unknown. Antipsychotic treatment is not a prerequisite for the occurrence of dyskinetic movements and they can be informative of outcome that worth to further explore.

1.9.2 Movement abnormalities and conversion to psychosis

In recent years, longitudinal studies of association movement abnormalities and the development of psychosis have been carried out. Mittal et al conducted a study on the conversion to axis I psychosis among prodromal adolescents and the predictive value of the movement abnormalities. Following initial assessment, participants were evaluated at four times annually. Ten subjects out of 40, developed axis I psychosis through a four-year period. Groups did not differ on demographic characteristics or

levels of prodromal symptomatology, but those who converted exhibited significantly more movement abnormalities. Movement abnormalities and prodromal symptoms were strongly associated and logistic regression analyses indicating that abnormalities in the face and upper body regions were most predictive of conversion. Again, the link between movement abnormalities and psychotic disorders is presumed to reflect common neural mechanisms that influence both motor functions and vulnerability to psychosis. Findings suggest that individuals with more movement abnormalities may represent a subgroup of prodromal adolescents who are at the highest risk for conversion (Mittal & Walker, 2007).

In another study, the same authors (Mittal, Neumann, Saczawa, & Walker, 2008) examined the longitudinal progression of movement abnormalities in adolescents at risk for developing schizophrenia. Thirty-two schizotypal personality disorder patients (which were considered patients with a high risk for conversion) were compared with other considered non-at-risk for psychosis such as other personality disorders and non-clinical control subjects (N=121 subjects). High-risk adolescents exhibited elevated frequency of movement abnormalities (dyskinesias in oro-facial and upper limb areas) and showed significant increase over time in comparison with clinical and nonclinical controls. The magnitude of relationship between symptoms and movement abnormalities increased throughout the course of the prodromal period. They hypothesized that vulnerability to psychosis involves striatal abnormalities, that can be initially manifested as movement disorders during childhood and adolescence, and later later manifested as prodromal or even psychotic features, once the maturated process in fronto-striatal circuitry in late adolescence takes place. The association dyskinesia with structural striatal abnormalities with smaller putamen volumes in the schizophrenia spectrum (Mittal et al., 2013) is consistent and fits into this framework.

Movement disorders seem that not only are associated to the psychiatric disorder, but to dynamically parallel changes in the clinical expression of conversion from prodromal to the psychotic episode.

1.9.3 Movement disorders and psychiatric outcome in first episode of schizophrenia

Very few studies of outcome in First Episode of Schizophrenia Spectrum disorders have included variables of movement disorder and assessed them with adequate instruments. In the few studies that included them, results generally show relationship with outcome. Chen 2013 found that MDI change of movement disorders was associated to outcome (Chen et al., 2013).In the European First-Episode Schizophrenia Trial (Eufest) using Sct Hans movement disorders scale found akathisia associated to twelve months outcome of the patients (Derks et al., 2010).

2   JUSTIFICATION

In the last years a clear progress has been made to advance the time of recognition of schizophrenia and the risk and prodromes of the disorder itself in order to implement treatment as early as possible, to reduce their consequences and to maximize the best possible outcomes. However, such a step forward has not paralleled with the early identification of those patients who will become less responsive and might be candidates to third line treatments.

There is converging data on a possible relationship on early movement disorders in schizophrenia and severity or refractoriness, but they are not systematically nor specifically investigated with appropriate instruments.

The aim of the present work is to study the association of early occurrence of dyskinetic movements with one-year outcome in a sample of First Episode of Schizophrenia Spectrum Disorders (FES) treated with SGA. FES is a more specific group of disorders compared to those included under the diagnostic group of First-Episode Psychosis (FEP). Therefore, FES patients allow a more accurate study of clinical and movement risk-factors linked to schizophrenia.

Early implementation of third-line therapeutics, which is normally postponed to later stages of the illness when patients have already shown refractory schizophrenia, may reduce the negative consequences of long periods of severe illness burden.

3 HYPOTHESES

Dyskinetic movements in first episode of psychosis patients are associated with worse clinical outcomes after one year of follow-up.

Dyskinetic movements and tardive dyskinesia can appear during the first year of treatment with Second Generation Antipsychotics (SGA).

4 OBJECTIVES

4.1 MAIN OBJECTIVE

To study the relationship of dyskinetic movements and other relevant variables with one-year outcome of first-episode schizophrenia-spectrum disorder.

4.2 SECONDARY OBJECTIVES

To determine the incidence of dyskinesia in a sample of first-episode schizophrenia-spectrum disorder patients during the first year of treatment.

To determine the incidence of Tardive Dyskinesia during the first year of treatment in the sample.

5   METHOD

5.1   DESIGN

This is an observational, longitudinal, prospective study of the association of dyskinesia and the severity of the first episode of a schizophrenic-spectrum disorder (FES) at one-year follow-up. The study was conducted at the Zucker Hillside Hospital, and the Bronx-Lebanon Hospital, which are two not-for-profit facilities in New York, NY, USA.

Data for this study were collected from November 1998 to October 2004, as part of the First Episode Study of Schizophrenia at Hillside Hospital in New York City (NYC). Previously, the results from a study comparing four-months outcomes of treatment with two classes of SGA drugs, risperidone and olanzapine, were published (Delbert G. Robinson et al., 2006). Afterwards, FES patients who were included in this study were followed-up for an indefinite period of time keeping the structure of systematic assessments focused on psychiatric and movement disorders outcomes.

For the present study, the follow-up was determined to up to one year so as to investigate the impact of early appearing movement symptoms. In addition, with this period of follow-up, the expected dropout rates were still not excessive to allow analysis.

5.2   SUBJECTS

The sample of the present study included patients suffering from their First-Episode Schizophrenia Spectrum disorder. This spectrum includes the diagnosis of schizophrenia, schizophreniform disorder and schizoaffective disorder.

Firstly, complete description of the study was facilitated and written informed consent was obtained from all adult subjects and, if available, from a family member. For subjects less than 18 years old, written parental consent and written subject assent was obtained. The study was approved by the Ethical Committee of Zucker Hillside Hospital, and it was based on the principles of the Declaration of Helsinki.

Inclusion criteria for the participation in the study were:

Current diagnosis of DSM-IV schizophrenia, schizophreniform disorder, or schizoaffective disorder within the schizophrenia spectrum disorders; age between 16 and 40 years old; less than 12 weeks of lifetime antipsychotic medication treatment; current positive symptoms evidenced by a rating of 4 or more on the severity of delusions, hallucinations, or thought disorder items of the Schedule for Affective Disorders and Schizophrenia Change Version with psychosis and disorganization items (SADS-C+PD) (Spitzer and Endicott 1978) or current negative symptoms demonstrated by a rating of 4 or more on the affective flattening, alogia, avolition, or anhedonia global items of the Hillside Clinical Trials version of the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1989; D. Robinson, Woerner, & Schooler, 2000); for women, a negative pregnancy test and agreement to use a medically accepted method of birth control.

Exclusion criteria were:

Meeting DSM-IV criteria for a current substance induced psychotic disorder, psychotic disorder due to a general medical condition, or mental retardation; medical condition/ treatment known to affect the brain (such as systemic and endocrine-metabolic conditions, neurodevelopmental, traumatic, tumor, muscular and nervous disorders, as well as use of corticosteroids, antiemetics, antihistaminergic drugs); any medical condition requiring treatment with a medication with psychotropic effects; medical contraindications to treatment with olanzapine or risperidone; or significant risk of suicidal or homicidal behavior. In this case the patient would be considered to require an intensive and much tailored approach. For example, the need of antidepressants or antipsychotics in high doses or Electroconvulsive therapy (ECT) which could represent a different subpopulation of FES with additional differences in treatment and subsequently confounding results.

5.3 STUDY VARIABLES

A Personal Data Inventory (PDI) was collected for: socio-demographic variables (age, sex, race, civil status, type of family) which included occupational and educational level reached by the patient and socioeconomic status; patient psychiatric history, including use of drugs; and family psychiatric history (see annex 1). Personal

Data Inventory was administered at baseline by interviewing patient and relatives of reference.

5.3.1 Socio-demographic variables

Occupational and educational level and socioeconomic status reached by the patient were used as proxy of the level of premorbid adjustment using the Hollingshead Index of Socioeconomic Status. The Hollingshead two Factor Index of Socioeconomic Status (SES) (see annex 2) is a survey designed to measure social status attained by the patient and the head of household which is based on two domains, educational and occupational level attained (Hollingshead, 1957, 1971). Higher SES values reflect lower levels of education or occupation. Parental occupation and education were coded using a seven-point scale ranging from 1 (higher executives, proprietors, major professionals; professional degree) to 7 (unskilled employees; less than seven years of school) based on Hollingshead's index of social position. Index of Social Status is based on the formula ((occupation score x 7) + (education score x 4)).

5.3.2 Psychiatric history

Patient psychiatric history included: age at first psychiatric symptom, age at first psychotic symptom, age at first psychiatric treatment, alcohol use, other drug use, suicidal behavior, duration of psychiatric symptoms until study recruitment. Duration of psychotic symptoms until study recruitment was used as duration of psychotic symptoms.

Family psychiatric history included: psychiatric diagnosis in first degree relatives and type of disorder or suicide, number of family members who were admitted at least once in a psychiatric ward.

5.3.3 Psychiatric diagnosis

Subject diagnoses were performed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First, Spitzer, Gibbon, & Williams, 2002). The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM; SCID) is a semi-structured interview which aims to determine whether a subject meets specific criteria for any DSM disorder.

5.3.4 Clinical psychiatric assessment

Clinical Global Impression (Guy, 1976) is a tool which provides a global rating of illness severity. The CGI is rated on a 7-point scale, with a range of scores depending on the severity of illness from 1 (normal) through to 7 (amongst the most severely ill patients). Similarly, when applied to improvement and response to treatment, either globally or in specific domains as positive symptoms CGI-C scores range from 1 (very much improved) through to 7 (very much worse).

Clinical Global Impression assessment was completed every week during inpatient stay for one month and then every two weeks for the first 4 months and every 4 weeks afterwards.

5.3.5 Movement disorder assessment

Movement disorders were assessed by means of the following assessment tools:

Simpson Dyskinesia Scale (SDS) (Simpson, Lee, Zoubok, & Gardos, 1979) for dyskinetic movements. Simpson Dyskinesia Scale was originally published by George Simpson et al. in 1979. It was designed specifically for dyskinetic movements and Tardive Dyskinesia, being widely used. It covers specifically each body area rating (facial and oral with typical face, lips, jaw, tongue movements, neck and trunk, upper and lower extremities, entire body and global overall tardive dyskinesia rating). Rating 0 to 5 from absent to severe movement (see annex 3). A special consideration is facilitated to most common and complex localizations, that is orofacial areas. Simpson Dyskinesia Scale assessments were performed at baseline and then every two weeks for the first 4 months and every 4 weeks afterwards. Any rating different from zero (absence of dyskinetic movement) were considered dyskinesia-positive patients.

Simpson-Angus Rating Scale for Extrapyramidal Movements (SAS) (Simpson and Angus 1988). Simpson–Angus Rating Scale for Extrapyramidal Disorders cover nine parkinsonian extrapyramidal signs and also one item for akathisia and cooperativeness. Eleven items rated 0 to 4 (gait, arm dropping, rigidity of major joints, tremor, salivation, akinesia, akathisia), 0 to 2 (balance, cogwheeling, glabella tap) or 0 to 3 (cooperativeness) (see annex 4). It combines specificity with simplicity and reliability (Janno, Holi, Tuisku, & Wahlbeck, 2005). Simpson-Angus Extrapyramidal

Rating Scale assessments were completed at baseline and then every two weeks for the first 4 months and every 4 weeks afterwards. Highest ratings during the first eight weeks were taken as variable to rate the most subacute symptoms, such as parkinsonian signs like akinesia, hypokinesia, rigidity and gait abnormalities, which could appear after the first few weeks.

Barnes Akathisia Scale for Akathisia (BAS) (T. R E Barnes, 1989; Thomas R.E. Barnes, 2003) covers both main components of akathisia, subjective, with two items rating awareness and distress related to restlessness, and objective, rating the movements in it selves. Ratings range from zero to three. Finally, an overall assessment of the disorder ranges from zero to five. It is easy to use, and complete (see annex 5). All them have good metric properties and is widely used (Thomas R.E. Barnes, 2003). For the purpose of the study, only the global rating was taken into consideration. Barnes Akathisia Scale assessments were completed at baseline, every week for the first month, every two weeks for the first 4 months and every 4 weeks afterwards. Highest global akathisia ratings in the first two weeks were considered.

Sensitivity of all movement disorders has been prioritized. For this reason, cut-off value of rating scales assessment has been defined at zero in parkinsonism, akathisia or dyskinesia.

5.3.6   Criteria for the diagnosis of Tardive Dyskinesia

The need of operational criteria to establish the diagnosis of Tardive Dyskinesia is particularly important when studying dyskinetic movements because they frequently wax and wane over time. The incidence rate of Tardive Dyskinesia was determined as probable according to the Schooler and Kane Research Criteria (SKRC) (N. R. Schooler & Kane, 1982), which entail severity, extension and persistence of dyskinetic movements together with antipsychotic treatment for at least three months (see annex 6). Therefore, the incidence of TD was considered as a cumulative measure along the study period.

5.4   TREATMENT PROTOCOL

Patients were randomly assigned to treatment with olanzapine or risperidone. The initial daily dose considered the fact that patients were naïve or less than 12 weeks of

lifetime exposure to antipsychotic drugs. It was stablished an initial dose of 2.5 mg for olanzapine and 1 mg for risperidone. It was sought to establish the lowest effective dose. A random assignment with open-label treatment was used. A slowly increasing titration schedule was used: after week 1, dose increases occurred at intervals of 1–3 weeks until the subject improved or reached a maximum daily dose of 20 mg of olanzapine or 6 mg of risperidone (see also Robinson et al 2006).

Lorazepam was given for agitation requiring pharmacological treatment. Sertraline for depressive symptoms and divalproex sodium for manic symptoms could be prescribed in the case of persistence and unresponsiveness to the antipsychotic drug. When parkinsonian symptoms and akathisia appeared as side effects of antipsychotic treatment, they were treated with the antipsychotic dose reduction or, if this was ineffective then benztropine for extrapyramidal symptoms and lorazepam or propranolol for akathisia was prescribed.

Dose of antipsychotic SGA was converted to olanzapine equivalents. Equivalency ratio at lower doses is different from these at higher doses. Formula applied is the mean of the lower and higher dose conversion factors. Conversion to methods: dose of risperidone x 2.9 = dose of olanzapine. Dose during the first month of treatment was then calculated in order to assess the initial need for higher antipsychotic potency to get symptom improvement.

5.5   STATISTICAL ANALYSES

Categorical variables are described as frequencies, and percentages and quantitative variables are described as mean and standard deviation, depending on variable distribution. In the univariate analyses of categorical variables, Chi-square test or Fischer exact test has been used, depending on application conditions. In the bivariate analyses of quantitative variables, the U Mann-Whitney non-parametric test was used. Survival analyses were evaluated with the Kaplan-Meier method so as to determine the potential effect of sex and treatment on the course of dyskinesia (event was defined with an SDS score above 0).

Lineal regression model, enter method was used. Variables were selected for inclusion in the multivariate regression analysis on the basis of 1) previous research

indicating their association with severity of illness (CGI-S) at follow-up (i.e., highest occupational status achieved, age at first psychotic symptom, CGI early global improvement at four week, Dyskinesia SDS rating in the first twenty-first weeks of at least one, Simpson and Angus Extrapyramidal Scale highest rating showed in the first eight weeks or 2) bivariate results (i.e., p-value ≤ 0.05 and effect size of Pearson's or Spearman's r ≥ 0.3 [medium]; sex, use of alcohol). Significance was set at p < 0.05 for all the analyses. The SPSS 22.0 package (SPSS Inc., Chicago, IL) was used to perform the statistical analyses.

6   RESULTS

Four hundred seventy-four patients were initially assessed for eligibility and one hundred twenty of them were included in the study for assignment to either risperidone or olanzapine as can be seen in the flow chart (see figure 1).

Figure 1 Flow-chart of patients from initial assessment to on-year follow-up.
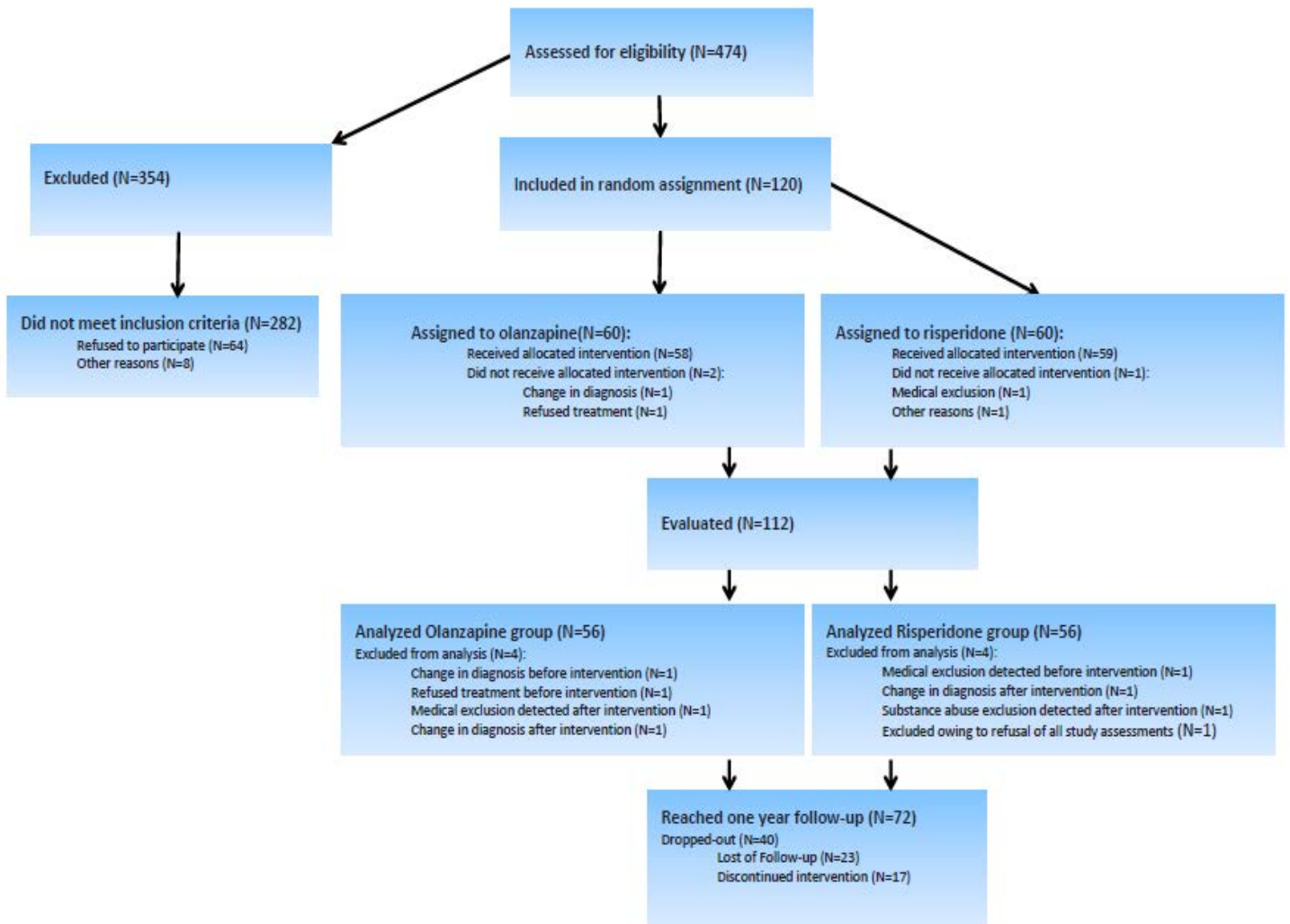
One hundred and twelve patients were finally included in the analysis. From these, seventy-two patients could be followed-up during the 12-month study length, allowing a variation of +/-4 weeks for the last evaluation. Forty patients dropped-out during this period. Twenty-seven were lost in follow-up and in seventeen cases the intervention was discontinued (please see below a comparison between non-completer patients and completers).

6.1 DESCRIPTION OF THE SAMPLE

6.1.1 Sociodemographic characteristics at baseline

Patients included in the study were predominantly young with a mean age of 23 years, ranging 16 to 38 years old, which is the expected range of onset of schizophrenia spectrum disorders. Seventy per cent of the patients were male, while only thirty percent were female.

Concerning race, half of the sample was African/American, twenty percent Caucasian, thirteen percent Hispanic, six percent were Asian and the rest were from other races. Patients were living non-independently in their clear majority (85%), either with parents or other family members, whereas only 15% were living by their own. Similarly, ninety per cent of the patients had never been married.

Mean patient's highest educational level was in the medium level range of studies corresponding to from a level of 9th Junior high school – Partial high school 10-11th (14a), to a level of High school graduate (18a) or Partial college for more than one year or specialized training (3 to 5 Hollingshead's Educational Level).

Mean highest occupational level of patients was in the medium-low level range of occupational levels corresponding to skilled manual employees.

Most families of the patients included were in the lower to middle socioeconomic status according to their household's head Hollingshead socio-economic status classification (see annex1).

Noteworthy, mean education and socioeconomic status of the patients were lower to that of their household head. Fifty-three per cent of the patients but only 19% of their head of household status were higher from status five. This represents an inversion in the direction of trans-generational change of status.

Table 1. Description of the sample: sociodemographic characteristics (N=112)

Age Mean (SD)	23.4 (5.0)
Gender (Female/Male)	34 (30.4)/ 78 (69.6)
Race	
Caucasian	22 (19.6)
African-American	60 (53.6)
Hispanic	15 (13.4)
Asian	7 (6.3)
Other	8 (7.1)
Civil Status	
Never married	99 (89.2)
Been married (current or past)	12 (10.8)
Type of family	
parental/collateral	95 (85.6)
conjugal/alone	16 (14.4)
Patient Hollingshead Status Mean (SD)	56.5 (12.8)
Head household Hollingshead Status Mean (SD)	41.7 (15.2)
Patient highest Occupational Level Mean (SD)	5.85
Head household highest Occupat. Level Mean (SD)	3.89

Note: values represent number and percentages or otherwise specified
Abbreviation: SD= Standard Deviation, Occupat.= Occupational

6.1.2   Psychiatric history

6.1.2.1   Family psychiatric history

Only in twenty percent of the patients there was a psychiatric family history in any of their first-degree relatives. In sixteen per cent of the patients there were family history of Schizophrenia, in eleven per cent there were of Affective Disorder, and in twenty-five per cent a family history of Abuse of Drugs was observed. One quarter of the patients at least one first-degree family member had to be hospitalized in a psychiatric ward.

6.1.2.2 Patient psychiatric history and current illness

The clinical ratings of Severity of Illness at baseline were "marked or severely ill" according to the CGI severity of illness assessment. Subjects had showed psychiatric symptoms in different degrees for more than four years before study entry whilst they showed psychotic symptoms for an average of more than two years, before commencement of the study. At study entry, eighty-seven subjects (78%) were antipsychotic naive, and 15 (13%) had only 1 to 7 days of lifetime antipsychotic medication treatment. Subjects showed predominant positive symptomatology with delusions and hallucinations which had a significant effect on behavior with ratings close to five. Negative symptoms were only rated as mild to moderate.

Table 2. Baseline psychiatric characteristics (N=112)

First Degree Family Psychiatric History Mean (SD)	
Schizophrenic Disorder	17 (16)
Affective Disorder	12 (11.5)
Abuse of Drugs Disorder	25 (23.8)
Psychiatric Hospitalization	23 (21.9)
Suicide (consumed)	12 (11.2)
Patient Psychiatric History and Current Illness Mean (SD)	
Age at first Psychiatric Symptom	18.88 (5.8)
Age at first Psychotic Symptom	21.02 (4.7)
Age at first Psychiatric Treatment	20.72 (5.6)
Duration Psychiatric Sympt. before rand (w)	220.6 (252)
Duration Psychotic Sympt. before rand (w)	112.98 (158.0)
Suicide Attempt N (%)	11 (10)
Baseline CGI Severity of Illness Mean (SD)	5.6 (0.6)
Use of Drugs N (%)	
Abuse of Alcohol	
Never	79 (71.8)
Not in the last year	14 (12.7)
Yes	17 (15.5)
Abuse of Other Drugs	
Never	61 (55.5)
Not in the last year	11 (10)
Yes	40 (34.5)

Note: values represent number and percentages or otherwise specified
Abbreviation: SD= Standard Deviation, w= week, Sympt= symptomatology, rand= randomization, CGI= Clinical Global Impression

Early global improvement of patients was measured at week 4, and the results showed that mean score on the CGI was 3.14 (SD=0.71) showing a modest change from baseline. By contrast, severity of illness CGI at the end of the study (12-month visit) was significantly reduced (p= <0.001). However, there was a significant association between global improvement at week 4 and severity of illness at month 12 (see bivariate analysis below). Along the study, eighty-four patients (75%), met DSM IV criteria for schizophrenia, 19 (17%) for schizophreniform disorder and only nine (8%) for schizoaffective disorder.

6.1.3 Comparison between Non.completers and Completers

To further study potential differences between non-completers and completers a univariate analysis was performed. It showed that female sex was significantly associated with less follow-up completion. Patients living non-independently (parental and collateral families) completed follow-up in a significantly higher proportion than those living alone or in couple. Neither race, civil status, educational or occupational highest level achieved by patient or head of household Hollingshead status resulted significantly associated with one year follow-up completion (table 3).

Table 3. Comparison non-completers vs completers at baseline (N=112)

	Non completers (N=40)	Completers (N=72)	p
	n (%)/Mean (SD)	n (%)/Mean (SD)	
Age (y)	24,1 (5.4)	22,96 (4.7)	ns
Gender			0.032
Female	17 (42.5)	17 (23.6)	
Male	23 (57.5)	55 (76.4)	
Race (African-American)	26 (65)	34 (47.2)	ns
Civil Status	35 (89.7)	64 (88.9)	ns
Type of Family			0.003
Parental/collateral	28 (71.8)	67 (93)	
Conjugal/alone	11 (28.2)	5 (6.9)	
Patient Hollings. SES	56,79 (14.1)	56,36 (12.1)	ns
HH Hollings. SES	43,52 (16.4)	40,81(14.6)	ns
Patient highest Occupational level	5.85 (1.5)	5.86 (1.4)	ns
HH highest Occupat. level	4 (1.7)	3.85 (1.6)	ns
First degree Family Psychiatric Antecedents			
Any psychiatric ant.	30 (75)	59 (81,9)	ns
Schizophrenia	7 (17.5)	10 (13.9)	ns
Baseline CGI Severity of Illness >5	5.6 (0.7)	5.54 (0.6)	ns
Abuse of Alcohol (never)	30 (78.9)	49 (68)	ns
Abuse other drugs (never)	22 (57.9)	39 (54.2)	ns

Abbreviations: HH= Head of Household, Hollings.=Hollingshead SES= Hollingshead socioeconomic status, CGI= Clinical Global Impression

6.1.4 Comparison between Female and Male patiens

Following the same rationale, differences in socio-demographic and clinical characteristics depending on sex were analyzed (table 4).

Table 4. Comparison of sociodemographic and psychiatric characteristics between female and male patients (N= 112)

	Female (N=40)	Male (N=72)	p
	n (%)/Mean (SD)	n (%)/Mean (SD)	
Age (y)	24.6 (4.8)	22.81 (5.0)	ns (0.08)
Race (African-Americ.)	22 (64.7)	38 (48.7)	ns
Civil Status (married)	7 (21)	5 (6.4)	ns (0.59)
Type of Family			0.003
Parental/collateral	21 (63.6)	74 (94.8)	
Conjugal/alone	12 (36.3)	4 (5.1)	
Patient Hollingshead SES	52.12 (14.3)	58.39 (11.6)	0.018
HH Hollingshead SES	41.35 (14.5)	41.78(15.6)	ns
Patient highest Occupational level	5.39 (1.6)	6.05 (1.3)	0.025
HH highest Occupational level	3.91 (1.7)	3.89 (1.6)	ns
First degree Family Psychiatric Ant.			
Any	26 (76)	63 (81.8)	ns
Schizophrenia	6 (19.3)	11 (14.6)	ns
Age at onset (y)	23.09 (5.00)	20.13 (4.4)	0.002
Duration of psychiatric symptoms before rand. (w)	67.09 (96.1)	132.65 (174.9)	0.046
Baseline CGI Severity of Illness >5	5.62 (0.7)	5.53 (0.6)	ns
Abuse Alcohol (never)	29 (87.9)	50 (64.9)	0.032
Other drugs (never)	23 (69.7)	38 (49.3)	0.017

Abbreviations: HH= Head of Household, Hollings.= Hollingshead, SES= Socioeconomic Status, Ant= Antecedents, CGI= Clinical Global Impression, w=weeks, y= years

As it can be seen in table 4, statistically significant results showed that more women were living by their own (independently), had more social status, but completed follow-up in a lesser proportion. In addition, they were older when they had the first psychotic symptom, with a shorter duration until first treatment and had less alcohol and drug abuse antecedents.

6.1.5 Comparison between Olanzapine and Risperidone

Also, initial drug assignment, Olanzapine or Risperidone, was analyzed. It showed no significant differences in socio-demographic or clinical variables. They do not seem to differ significantly in the occurrence of dyskinetic movements (table 5).

Table 5. Comparison of sociodemographic characteristics between patients initially treated with Olanzapine or Risperidone (N= 112)

	N(%) / Mean (SD)		p
	Olanzapine	Risperidone	
Age (y)	23.31 (4.5)	23.41 (5.5)	ns
Gender (female)	15 (27.2)	18 (31.0)	ns
Race	-	-	ns
Civil Status (married)	47 (85.4)	51 (92.7)	ns
Type of Family			ns
Parental/collateral	47	48	
Conjugal/alone	8	7	
Patient Hollingshead SES	55.04 (12.3)	57.80 (13.2)	ns
HH Hollingshead SES	40.77 (14.3)	42.31 (16.3)	ns
Patient highest Occupat. level	5.67 (1.5)	6.02 (1.4)	ns
HH highest Occupat. level	3.78 (1.58)	3.98 (1.7)	ns
First degree Family psychiatric ant.			
Any	42 (77.8)	46 (82.1)	ns
Schizophrenia ant.	9 (17.0)	8 (15.1)	ns
Age at onset (y)	21.67 (4.8)	20.47 (4.7)	ns
Duration of psychotic symptoms before rand. (w)	85.53(104.2)	247.60 (280.4)	ns
Suicidal attempt	2 (3.7)	9 (16.4)	ns
Abuse of alcohol			ns
Never	37 (68.5)	41 (74.5)	
Abuse other drugs			ns
Never	26 (48.1)	31 (59.6)	
Equivalent dose of assigned drug	11,04 (5.1)	9.01 (3.5)	ns
Baseline CGI severity of illness			ns
>5	29 (53.7)	29 (51.8)	

Abbreviations: w= weeks, y= years, Occupat.= Occupational, HH= Head of Household, Hollings.=Hollingshead, Ant.= Antecedents, SES= Socioeconomic Status, CGI= Clinical Global Impression

6.2 STUDY VARIABLE: MOVEMENT DISORDERS

6.2.1 At baseline

Ratings of movement disorders at baseline using the specific assessment scales in dyskinesia, akathisia and parkinsonism, were very low. Fifteen patients (13%) showed dyskinetic movements using Simpson Dyskinesia Scale (SDS). Eleven minimal or doubtful, three mild dyskinesia and one patient showed moderate dyskinesia. Regarding parkinsonism, Simpson and Angus Rating Scale for Extrapyramidal Symptoms (SAS) mean rating was 1.14 (SD= 1.56), which indicated that parkinsonism was almost absent. Similarly, mean global score on the Barnes Akathisia Scale (BAS) was low (0.34, SD= 0.69), i.e. absence of akathisia at baseline.

When comparing differences in follow-up completion, sex and treatment assignment, the results showed that groups were comparable (p= >0.05) in terms of dyskinetic movements, parkinsonism or akathisia.

6.2.2 At follow-up

6.2.2.1 Dyskinesia

Forty-one patients showed ratings of dyskinesia of one or more according to the Simpson Dyskinesia Scale (SDS) during the one-year follow-up. One patient was rated as moderate dyskinesia, eight mild and twenty-three minimal or doubtful. Thirty-two of them appeared in the first twenty four weeks and nine from week twenty-four to the one-year follow-up.

6.2.2.2 Parkinsonism

Mean Simpson and Angus Scale (SAS) rating, which was 1.14 at baseline visit, increased to a maximum of 2.35 during the first two weeks, as SGA dose were also increased. During the first eight weeks ratings reached a mean maximum of 3.29. Once antipsychotic treatment is initiated SAS ratings increased two to three-fold.

6.2.2.3 Akathisia

Mean value of the highest Barnes Akathisia Scale (BAS) global ratings during the first two weeks were 0.66, being absent or mild for 78% of the patients. Mean ratings were increased two fold from 0.34 in the basal visit.

6.2.2.4 Tardive Dyskinesia

Six patients reached Schooler and Kane Research diagnostic criteria for Tardive Dyskinesia during the first year of treatment. All of them were followed up until the last follow-up visit. An incidence of 5.35 % out of the 112 patients who initiated the study, and 8.3 % out of the 72 patients which completed was observed.

6.3 STATISTIC ANALYSIS

6.3.1 Bivariate analysis

Bivariate analysis of socio-demographic and psychiatric characteristics with outcome measure (i.e., mean score in CGI severity of illness) showed that global improvement at week four, male sex, abuse of alcohol and other drugs, Hollingshead socioeconomic status of patient and head of household were significantly associated with one-year outcome. Neither age, duration of untreated psychosis or ratings of parkinsonism, akathisia or dyskinesia showed significant association with one-year outcome (see table 6).

Table 6. Bivariate analysis results of comparison of psychiatric and movement disorders outcome after one year of follow-up (n=112 at baseline vs 72 at follow-up, paired data)

|	Stadistics	
	R	p
Age	0.06	ns
Sex	0.31	0.008
Race	0.06	ns
Civil Status	-0.07	ns
Type of Family	0.21	ns
Patient's Hollingshead SES	0.23	0.049
Head household's Hollingshead SES	0.25	0.034
Patient highest occupational level	0.18	ns
Head household highest occupational level	0.21	ns
First Degree Family Psychiatric History (any)	0.07	ns
Patient Psychiatric History and Current Illness		
Age at first psychiatric symptom	0.08	ns
Age at first psychotic symptom	0.07	ns
Age at first psychiatric treatment	0.13	ns
Duration of psychiatric symptoms before rand (w)	-0.12	ns
Duration of psychotic symptoms before rand (w)	-0.01	ns
Suicidal attempt	-0.14	ns
Baseline CGI Severity of Illness	0.05	ns
Week 4 CGI Global Improvement	0.42	0.001
Abuse of alcohol	0.30	0.011
Abuse or Addiction Other Drugs	0.26	0.026
Movement Disorders Baseline		
Parkinsonism SAS	- 0.19	ns
Akathisia Global BAS	- 0.00	ns
Dyskinesia SDS	0.06	ns
Movement Disorders follow-up		
SAS 8 weeks	0.09	ns

BAS 2 weeks	0.01	ns
SDS 24 weeks	- 0.07	ns
SDS one year	0.12	ns

Abbreviations: CGI= Clinical Global Impression, SAS= Simpson-Angus Scale, BAS= Barnes Akathisia Scale, SDS= Simpson Dyskinesia Scale, SES= Socioeconomic Status, w= weeks, y= years

6.3.2 Survival analysis

Figure 2 illustrates the temporal profile of dyskinetic movements (SDS) along the study period. It can be observed that the appearance of movements was slightly more pronounced during the first weeks, and from week 24 (approximately) the number of patients presenting movements drew a plateau.

Figure 2 Dyskinesia Survival Curve
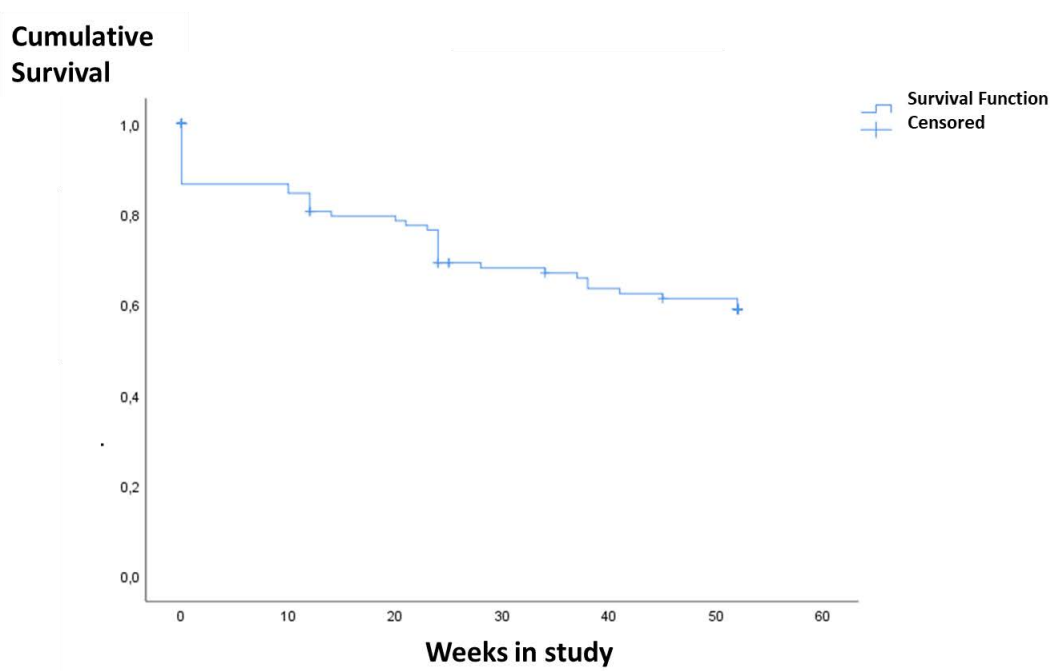
Cumulative dyskinesia survival curve depending on sex and treatment.

Figure 3 Dyskinesia survival curve in both sexes.

Cumulative Survival

Weeks in study
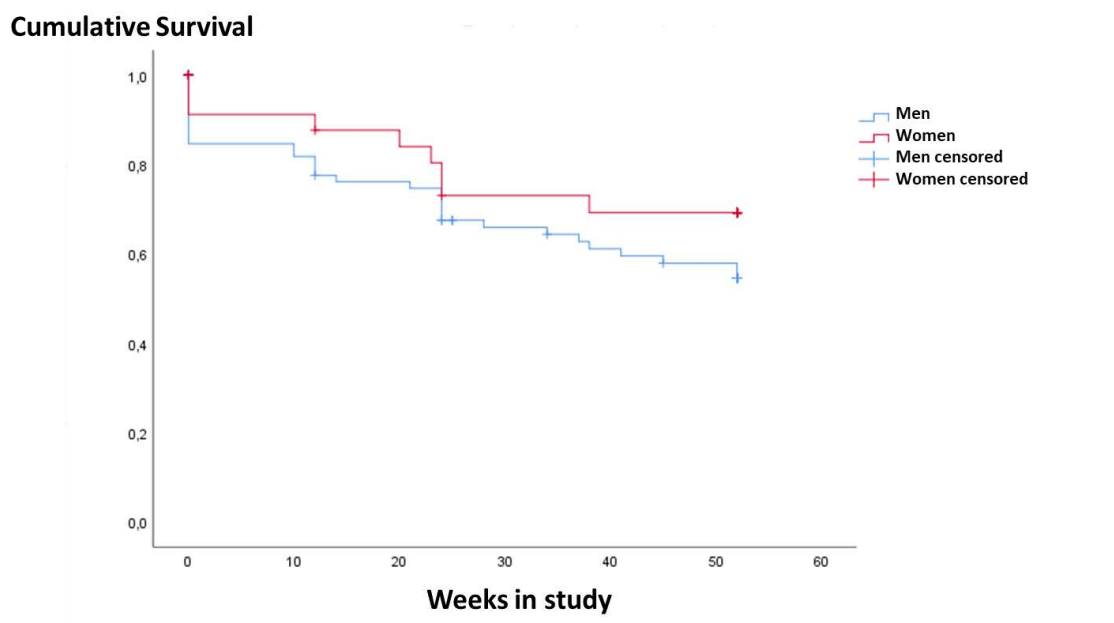
Male patients showed a higher risk than female patients. Sex does not seem to influence the shape of the survival curve.

Figure 4 Dyskinesia survival Curve in patients assigned to risperidone and olanzapine.

Cumulative Survival

Weeks in study
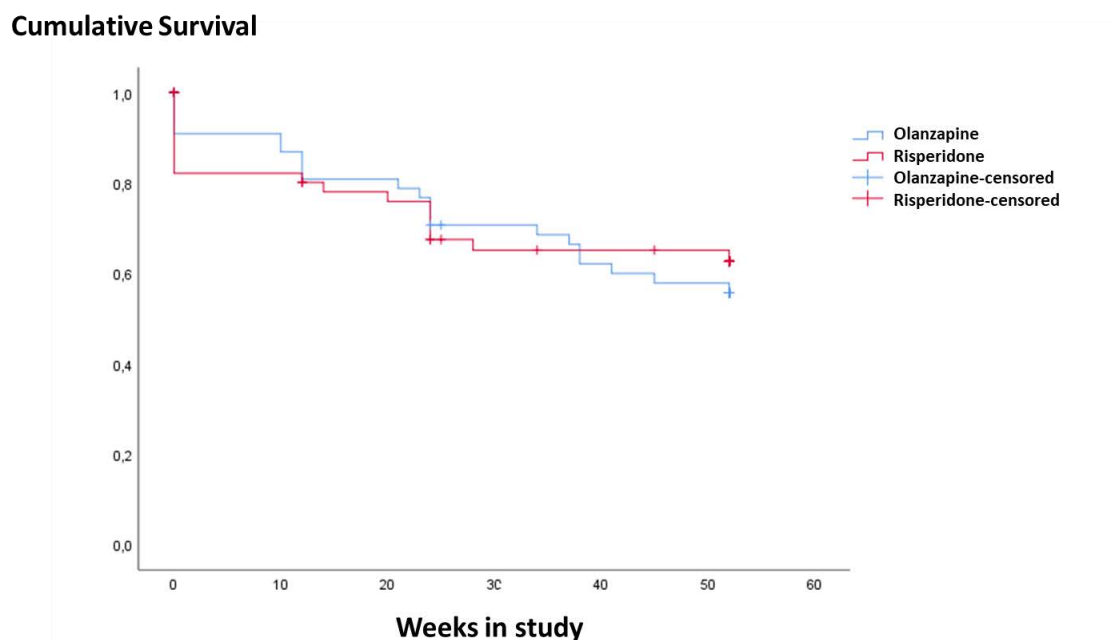
Initial assigned treatment risperidone or olanzapine although pharmacodynamically different, does not seem to significantly differ in the occurrence of dyskinetic movements (figure 4).

6.3.3 Multivariate analysis

The dependent variable was the score of the CGI severity of illness at one-year follow-up. The variables included in the linear regression model were sex, age at first psychotic symptom, CGI severity of illness at fourth week, highest occupational level reached, abuse of alcohol, highest SAS rate in first eight weeks and global SDS rating different form zero in first 24 weeks. Significance showed by the model is p< 0.001.

Linear regression model showed that dyskinetic movements during this 24 weeks period is significantly associated with lower severity of the schizophrenia spectrum disorder.

CGI severity of illness at fourth week, abuse of alcohol, highest occupational level, , age at first psychotic symptom, dyskinetic movements during first 24 weeks and Sex were significant variables in the multivariate model. Variance explained by this model (adjusted R2) is 0.416.

Table 7. Linear regression model enter method

	B	Stand error	β	t	p
(Constant)	-1.481	1.135		-1.305	0.197
Sex	0.633	0.298	0.269	2.121	0.039
Highest occupational level	0.197	0.089	0.267	2.211	0.031
Age at first psychotic symptom	0.066	0.030	0.272	2.19	0.033
SDS Dyskinetic movements first 24w	-0.538	0.248	-0.248	-2.174	0.034
SAS Highest Parkinsonism first 8w	0.035	0.056	0.069	0.631	0.531
CGI Global Improvement at 4w	0.566	0.159	0.368	3.549	0.001
Abuse of alcohol	0.225	0.098	0.251	2.292	0.026

Abbreviation: CGI= Clinical Global Impression

7 DISCUSSION

7.1 DYSKINESIA, OTHERS MOVEMENT AND OUTCOME

The main objective was to longitudinally study the association of dyskinetic movements with one-year severity of illness in the First Episode of Schizophrenia Spectrum disorder.

The linear regression model of outcome fitted early response (p= 0.001), abuse of alcohol (p= 0.026), higher occupational level reached (p= 0.031), younger age at onset (p= 0.033), dyskinetic movements during the first twenty-four weeks (p= 0.034) and female sex (p= 0.039), but not first eight weeks Parkinsonism, as significant variables. This model explains forty-one percent of the observed variance. (adjusted R² 0.416).

Parkinsonism, akathisia and unspecific movement abnormalities have been repeatedly associated to different parameters of bad outcome, more lifetime hospitalization and non-response (Kinon, Kane, Johns, et al., 1993; Kinon, Kane, Chakos, et al., 1993; Levinson et al., 1990; Owens et al., 1982). In this study, the hypothesis of an association of dyskinetic movements with more severity of illness at one-year follow-up was not confirmed. Moreover, it seems that according to our multivariate linear regression model dyskinetic movements during the first twenty-four weeks were predictive of less severity of illness at outcome in this sample of FES patients treated with SGA. Other movement disorders, Parkinsonism in the first eight weeks and Akathisia in the first two weeks failed to show any significant association with severity of illness at one-year.

Literature in this field show several limitations. They do not distinguish between dyskinetic movements from other kinds of movement disorders, mixing different types of movement disorders. In addition, psychotic samples are not in their first episode of psychosis or have not been treated exclusively with SGA, showing exposition to FGA, before or during the conduction of the study.

<u>Movement disorders and outcome in psychotic non-FES patients</u>

Chen et al 2013 studied non-FES patients, which were middle aged, received FGA and SGA and used the Movement Disorder Inventory (MDI) which is a composite of movement disorders; parkinsonism and other; and antiparkinsonian medication (Chen

et al., 2013). They found that worsening in their MDI was a marker of poorer prognosis at one-year outcome. In a study by Mittal et al. used specific tools for the assessment of dyskinesia, but subjects were adolescents at high-risk of psychosis.

In other studies, non-FES patients were treated with FGA or both FGA and SGA; study general neurological signs or extrapyramidal movement disorders related to hyper or hypodopaminergic state altogether without specific assessment tools; and were cross-sectional or retrospectively designed, being difficult to compare the results in the context of the present study.

<u>Movement disorders and outcome in FES patients</u>

Previous studies in FES patients have shown an association between movement disorders and extrapyramidal signs and worst outcome. Robinson et al examined treatment response of 118 patients but dyskinetic movements were not studied and patients were treated with FGA (D G Robinson et al., 1999).

Other studies of outcome in FES patients treated with SGA have taken movement disorders in consideration (Carbon & Correll, 2014; Derks et al., 2010; Díaz et al., 2013; N. Schooler et al., 2005; Stentebjerg-Olesen et al., 2013). Derks et al. did not include dyskinesia in their study of one-year remission (Derks et al., 2010). In Stenberjerg-Olesen et al. dyskinesia was not assessed, patients were children or adolescents naturalistically treated, many had comorbid mental syndromes, such as mental retardation, autism, and received potentially confusing additional medication (Stentebjerg-Olesen et al., 2013). In another study of one-year outcome in FES patients (Díaz et al., 2013), specific tools of dyskinesia movement or ratings were not used. In a study of movement disorders in FES patients (N= 39) a specific assessment of dyskinesia was included using specific assessment tool. Prevalence of dyskinesia was 13% after a single baseline rating of dyskinesia and it was not significantly associated with six-months outcome (Cortese et al., 2005).

In the present study dyskinetic movements have been distinguished from parkinsonism and akathisia and specific assessment tools have been used by trained and experienced raters in a longitudinal design. From the results of the present study, it can be postulated that dyskinetic movements could be the expression of the

dopaminergic system reactiveness in response to dopaminergic under activity due to the own regulation mechanisms in early psychosis and the use of antipsychotic drugs. The main action of any antipsychotic drug is the antagonism of dopamine receptors. The dopaminergic system escape reactivity with increase of turn-over in dopaminergic pathways (Post & Goodwin, 1975) would be consistent with this postulate.

<u>Other extrapyramidal movement disorders</u>

Highest Parkinsonism rating during the first two months of treatment was not associated with outcome. Given previous results of a positive relationship of Parkinsonism with better outcome (Cortese 2005), it could be expected that both Parkinsonism and dyskinesia would be correlated with better outcome, as successive phenomena in the basal ganglia. Hyperkinesia after hypoactivity of the dopamine system. But this succession would need of previous hypo dopaminergic action which are almost absent in baseline and during first two months of parkinsonism assessment in our sample.

Perhaps the fact that both extrapyramidal disorders were assessed before any antipsychotic administration did not allow checking the reactivity of the nigro-striatal system. Then, a static and transversal approximation to the movement was tested, lacking the hastening role of dopamine blocking effect on the extrapyramidal system exerted by antipsychotic drugs.

In addition, it makes a clear distinction with Dyskinesia, as expected form its pathophysiologic mechanisms are opposite and parkinsonism is due to dopaminergic low activity because of dopamine-antagonist drugs while dyskinesia is an indirect effect that would need the own reactiveness of the dopaminergic system to happen.

Global akathisia in the first two weeks did not show any association with outcome, but statistical power was lacking.

So far, published studies on movement disorders and outcome put any extrapyramidal disorder or even any neurological sign together in the same variable and call for the study of outcome prediction (Walther & Mittal, 2017). It gives at most a generic idea of the possible relationship of movement abnormalities in the outcome, with results depending on the proportion of every kind of movement disorder, if any.

Movement abnormalities may reflect a striatal pathology that of a shared neural circuitry for movement abnormalities, and psychotic symptoms (Cortese et al., 2005; Mittal et al., 2008). A deficit in neural plasticity related to DA has been proposed as a key pathophysiology mechanism in both schizophrenia and aberrant motor performance (Daskalakis, Christensen, Fitzgerald, & Chen, 2008).

Garver et al (2000) suggested three different endophenotypes in terms of outcome (good, delayed and non-response). They studied their dopaminergic activity and showed that good outcome is associated with excess in the dopaminergic activity, measured from DA metabolite: plasma homovanilic acid (HVA) (Garver, Holcomb, & Christensen, 2000), but they did not assessed dyskinetic movements.

Higher pretreatment levels of dopamine metabolite HVA, marker of dopaminergic release, have been associated with better therapeutic response and less likelihood of Parkinsonism (J. A. Lieberman et al., 1996) in the context of a larger dopamine disruption found in schizophrenia, particularly in motor basal ganglia (Horga et al., 2016; Winton-Brown et al., 2014) as well as in other dopaminergic pahways like tubero-infundibular dopaminergic regulation of prolactin in drug-free patients (Garcia-Rizo et al., 2012; Petruzzelli et al., 2018; Riecher-Rössler et al., 2013).

It could be speculated that after a first step of dopamine antagonism, the reactivity of the dopaminergic system in motor areas could lead to overcome this antagonism, clinically expressed as a dyskinesia. So, this indirect effect of hyper dopaminergic state, clinically dyskinesia, would be important indicative of the reactiveness of the system. The reversion of these dyskinesias by the administration of anticholinergic drugs or by reducing the dose of antipsychotics (Gerlach, 1979) is consistent with this statement.

Initial dyskinetic movements would be the result of the own dopamine system reactiveness either to antipsychotic treatment or to the own schizophrenia process (Marsden, Tarsy, & Baldessarini, 1975; Pearce & Clough, 1986). This reactiveness can be related to an increase in dopamine turn-over because of Dopamine D1 auto-receptor blockade by antipsychotic drugs. An elevation in striatal DA uptake predating the onset of schizophrenia in ultra-high-risk (UHR) patients have been shown by using Positron Emission Tomography (Howes et al., 2009). Later, changes in the post-synaptic membrane (Yoshida et al., 2014) would result in persistent Tardive Dyskinesia

(D Tarsy & Baldessarini, 1986). Dyskinetic movements showed in FES patients in this study would reflect the basal ganglia DA sensitivity to dopaminergic blocking drugs. So, these patients show better outcome at one-year follow-up. In longer follow-up it could be hypothesized that those patients who progress to persistent changes in their dopaminergic system, would show a fatigue of the dopaminergic system and clinically Tardive dyskinesia. It makes a fundamental difference in dyskinesia and tardive dyskinesia putative pathophysiological mechanisms.

7.2 OTHER EXPLICATIVE VARIABLES IN THE MODEL

7.2.1 Sex

Sex was a statistically significant factor both in the bivariate analysis and in the multivariate model. Male patients showed more severe illness at one-year follow-up. The results are consistent with other studies, showing that male patients are a factor related with poor outcome (Carbon & Correll, 2014) specially at one year or longer outcomes (Derks et al., 2010; Díaz et al., 2013; Gaebel et al., 2014; Selten et al., 2007).

One third of the sample were women. Compared with women more men completed follow-up. They were significantly not living independently, had lower social status, were younger at first psychotic symptom, which lasted untreated for longer time and had more alcohol abuse history at baseline. Perhaps overrepresentation of substance abuse or hidden factors such as adherence in men could explain part of the worst outcome referred in men. Also, a lack of help seeking behavior in men has postulated (Thorup et al., 2014) to explain sex differences in outcome. But seems unlikely in our sample where men are comparatively less living independently and there is usually a family member who would seek for help. Better explanations come from the role of estrogens as modulators of dopamine activity, in addition to global adjustment (M. V. Seeman, 1986). There is agreement In the literature in the fact that schizophrenia onset in women is three or four years later than in men and show better course until menopause due to the fading effect of estrogens in the perimenopause period (Hafner et al., 1998). This is consistent with the fact that antipsychotic dose needed by women are minor compared to men to achieve a similar occupancy of D2receptor (Eugene & Masiak, 2017).

7.2.2 Occupational level

Highest occupational level achieved was associated with outcome In our study. Occupational and educational level reached were used as proxies of the level of adjustment reached. it was decided to include patient highest occupational assessment in the model because occupation is a sensitive and complex variable due to the implicit combination of educational and social interaction adjustment. It worth to mention that socio-economic status of patients was lower than their respective household head. Although no definite conclusion can be drawn, patient premorbid adjustment could be one if not the main reason.The importance of previous adj ustment and achievements in terms of social, affective, scholar and occupational aspects of life have been previously studied and perhaps is the most replicated factor associated to outcome in schizophrenia (Rabinowitz et al., 2006). A consistent association between the general premorbid adjustment and outcome have been shown since a long time (Cannon-Spoor, Potkin, & Wyatt, 1982; Strauss & Carpenter, 1977). Low premorbid functioning is usually related to bad outcomes perhaps indicating subtle biological impairments that precede the onset of psychotic symptoms and also to increased movement abnormalities. At various development stages, Premorbid Adjustment Scale (PAS) areas such as sociability and withdrawal and mean total scores correlated with increased drug-induced parkinsonism and tardive dyskinesia (Strous et al., 2004). Measures of premorbid functioning could indicate that disease pathogenesis is manifest, albeit more subtly, prior to the presentation of the first psychotic symptoms.

7.2.3 Age

Younger age at onset was associated with lower severity at one-year outcome. In our sample range of ages at onset is relatively narrow. Females who had onset at older ages and had better outcomes, could affect the model. Another possible explanation is linked to confusion factor due to the abuse of drugs which could impair outcome in male patients. Younger age at onset has been a traditional variable associated with outcome and possibly it is due to neurodevelopmental abnormalities and the lack of chance to achieve further maturational steps in the development of youth. But, in a child and adolescent FES study Stenteberger et al. reported that older ages at onset

were associated with worst outcomes. Age at onset in our sample fits in the common age range of onset in psychosis and therefore more distant of highest neurodevelopmental periods. In a large study (N= 7000), Rabinowitz et al, found that younger age was associated with better responses although did not reach of statistical significance, when gender is represented evenly and have prominent symptoms (Rabinowitz et al., 2014). In a study of 304 patients. (Thorup et al., 2014) reported that earlier age and less negative symptoms at baseline and predicted better rates of recovery at 10 years later.

Perhaps the existence of different subgroups of patients and course that fits into schizophrenia diagnosis (Case et al., 2011) could explain this lack of consistency in the literature. In very young samples age at onset could represent those patients with more neurodevelopment abnormalities. But in older ages it does not follow necessarily the same pattern. Once this key steps of neurodevelopment have taken place the association of age of onset with outcome is reduced (Gureje & Bamidele, 1998).

7.2.4 Alcohol abuse

Abuse of alcohol resulted a significant factor in the model of association with severity at one-year outcome. This is an expected result as comorbidities and specially abuse of alcohol, impair outcome not only in Schizophrenia but also in high risk populations (Fusar-Poli et al., 2013). Abuse of alcohol is common in contemporary first-episode psychosis samples in the United States. Half of the FES patients have co-occurring substance use disorders, which are associated with both more severe symptoms and greater perceptions of stigma (Brunette et al., 2018). In the other hand, abusers, have been reported to be more socially active both premorbid and during the year preceding the start of treatment (Larsen et al., 2006), but this is a potential confounder that was not controlled.

7.2.5 Early response

The association of early response to treatment at week four with one-year outcome is consistent with many other studies in schizophrenia relapse and in first episode (Correll, Malhotra, Kaushik, McMeniman, & Kane, 2003; Derks et al., 2010; Stentebjerg-Olesen et al., 2013). Week four was considered clinically as a good period

time to anchor assessment being results clearly indicative of a robust association with one-year outcome. There is some debate on how early it can be used as a reliable prognostic factor in be response to treatment. Although two weeks is considered enough time, prediction of remission is significantly better at four or six weeks (Derks et al., 2010). The lack of significant correlation between severity of illness at baseline and dose of antipsychotic at week four with one-year severity stresses the idea of an inner reactivity of dopaminergic system as most important with outcome. Baseline level of psychopathology or doses of antipsychotic were not associated with outcome.

7.3   INCIDENCE OF DYSKINETIC MOVEMENTS IN THE SAMPLE

Forty-one patients of the initial FES spectrum sample (36,6%) showed dyskinetic movements at some point during the one-year follow-up and thirty-two of them during the first six months of treatment. This rate was higher than expected, perhaps due to the frequency of assessments and length of follow-up carried out which captures dyskinesia which tendency is to wax and wane.

Fifteen patients showed dyskinetic movements at baseline. Since there was no previous exposure to antipsychotics, they could be considered spontaneous dyskinesia. Rates of prevalence of spontaneous dyskinesia in naïve patients (or dyskinesia in absence of history of antipsychotic exposure) and acute dyskinesias (or initial hyperkinesia or Tardive-Dyskinesia-like) during initial treatment are scarce.

In naïve FES patients, a cross-sectional data reported thirteen percent prevalence of dyskinesia, although sample was small (N= 39) (Cortese et al., 2005). Lee reported that 0.3 percent of naïve patients in their FES showed spontaneous dyskinesia (J. Lee, Poon, & Chong, 2008) but the own authors postulate ethnical differences from their Asian patients to explain it. Data from studies of dyskinesia in FES naïve patients, showed a mean prevalence of four percent (Fenton, 2000).

In other studies of 15 to 50% have been reported (Fenton, 2000; McCreadie et al., 2005; Owens et al., 1982) but they include non FES patients. In a systematic review, a mean nine percent of patients showed spontaneous dyskinesia (Pappa & Dazzan, 2009).

The diversity of frequencies published, probably reflect the different design of the studies. Some come from the retrospective review of medical records with different samples in terms of length of illness, age, context (outpatient or institutionalized), and comorbid conditions. To what extend these movements reflect further liability to develop Tardive Dyskinesia is a remaining question, but the elevated proportion of patients who showed these abnormalities does not seems to support this possibility.

7.4 INCIDENCE OF TARDIVE DYSKINESIA

Six patients reached the Schooler and Kane Research Criteria for TD, that is 5.3% incidence in our FES patients treated with SGA sample and followed for one year. Due to drop-out of patients during the follow-up, data on rates of dyskinesia and tardive dyskinesia are necessarily conservative. Incidence among completers was 8.4 percent.

Chakos et al (1996) prospectively studied the incidence of persistent TD in a group of 118 FES patients. Persistent TD were diagnosed in 4,8% of the patients in the first year, but they were treated with FGA (Chakos et al., 1996). In the study by Oosthuizen et al., FES patients (Oosthuizen et al., 2003) seven out of fifty-seven (12,28%) subjects developed TD according to SKRC (N. R. Schooler & Kane, 1982), but patients were treated with FGA haloperidol and assessed only every trimester for Tardive Dyskinesia. Those who developed TD had a mean age of 37.1, had a longer duration of FES, or a later onset, representing perhaps a different form of schizophrenia. These authors reported that slightly more than 12% of patients developed TD (probable or persistent). But the sample was small, only 39 of the 57 patients were followed for the whole 12-month period. Schooler et al. they detected dyskinesia at baseline in a similar rate (N. Schooler et al., 2005) and emergent and persistent dyskinesia appeared during the three years follow-up were in 8.3% and 1.8% of the patients in the risperidone group, compared to 13.4% and 3.3%, respectively, in the haloperidol group (p=0.05 and 0.28). Those rates were lower than ours and could be attributed to the fact that dyskinesia at baseline were discarded as an strategy to select those dyskinesias induced by antipsychotic treatment and the strict criteria of Persistence Tardive Dyskinesia which needs of higher severity of movements.

This result adds some data on how the issue of Tardive Dyskinesia in the so-called SGA era is far from an end. It was supposed that with introduction of SGA any Tardive Dyskinesia would be a past concern. But it can be speculated to what extent it is related to the potential induction of TD by the diverse SGA, to the own pathological process in the individual patient or to the interaction of both. Other studies have focused either in long-term patients or samples with diverse length of illness. In addition, in these studies standardized and systematic examination protocol have not been used and are retrospectively or are transversally designed.

The problem of the sample selection is very important because patients who have been already exposed to antipsychotics face confounding risk factors, schizophrenia and movement outcomes. In addition, when a wide range of age is added, it is hard to know what is associated to age, to specific period of schizophrenia or to the characteristics of treatment.

7.5   SOME CONSIDERATIONS

After the introduction of antipsychotic drugs in the fifties, a link between them and extrapyramidal movement abnormalities were observed in both clinical and experimental settings and fueled an etiological association of any EPS to antipsychotic treatment in schizophrenia.

One of the problems associated to the study of dyskinetic movements and tardive dyskinesia is the implicit tautology in the definition of Tardive Dyskinesia as it includes previous antipsychotic exposure as criteria needed for diagnosis, instead of being just a risk factor for dyskinesia. The natural study of this clinical phenomenon becomes artifact by the amputation of part of the clinical reality which is its spontaneous emergence.

Most studies including clinical trials attributed EPS to treatment. But neurological symptoms in untreated schizophrenic patients show a relationship with the response to antipsychotic treatment (J. Lieberman et al., 1993; D G Robinson et al., 1999). The meaning of movement disorders including EPS as a window of dopaminergic functionalism and its relation to clinical outcome have been rarely studied despite clinical data supporting the presence of EPS in naïve schizophrenic patients. It stresses

the importance of dyskinetic movements as a prognostic factor in the one-year outcome in schizophrenia.

7.6   LIMITATIONS

Sample size is limited specially taken into account that there is probably more than one single subgroup under the label of First Episode Schizophrenia spectrum disorders.

Outcome length limited to one-year. Further prediction cannot be inferred from these results and probably the factors associated are different depending on the length of follow-up.

Sensitivity of assessments and specificity. The reliability of minimal movement disorder and low ratings could favour false positive dyskinetic movements. Nevertheless, genuine clinical characteristics of the movements with typical anosognosia, localization and characterisitcs of frequency and amplitude together with extensive qualification or raters, minimize this limitation.

Diskinesia vax and wanes along a given time period. For this reason a more frequent assessment of movement and clinical psychotic symptoms would be needed to get a more real pattern on the appearance and disappearance of dyskinetic movements.

Data on antipsychotic compound and dose after first month is missing, making possible associations to changes in dopaminergic antagonism in connection to movement disorder impossible.

More data on outcome of patients who were diagnosed of Tardive Dyskinesia compared to non-persistent dyskinetic patients will need of larger number of patients and longer follow-up.

In summary, the results show that dyskinesia is an independent variable associated to one-year outcome predicting less severity of illness together with early improvement and highest level of occupation achiever, younger age at onset and female sex. It can help in the decision of an as early as possible implementation of third line treatments.

Dyskinesia appears as early as in the first weeks of treatment and Tardive Dyskinesia appears in more than five percent of cases in our sample.

8   CONCLUSIONS

<u>Main Objective</u>

To study the relationship of dyskinesia movements and other relevant variables with one-year outcome of first-episode schizophrenia-spectrum disorder.

- Early Dyskinesia movements are associated with one-year outcome of the First-episode of Schizophrenia Spectrum Disorders.

<u>Secondary Objectives</u>

To determine the incidence of dyskinesia in a sample of first-episode schizophrenia-spectrum disorder patients during the first year of treatment.

- Forty-one patients, out of the one hundred and twelve who entered the study showed dyskinetic movements during the follow-up. Dyskinetic movements are frequent in FES patients.

To determine the incidence of Tardive Dyskinesia during the first year of treatment in the sample.

- Six patients out of the one hundred and twelve who entered the study showed dyskinetic movements during the follow-up. Incidence of Tardive Dyskinesia under Second Generation Antipsychotic treatment is 5.3 per cent in our FES sample.

<u>Further research</u>

To further characterize the reversibility of the dyskinetic movements in the medium and long-term and the patients who experiment progression to the appearance of Tardive Dyskinesia and their relationship with the severity of schizophrenia.

9 REFERENCES

Abi-Dargham, A., Gil, R., Krystal, J., Baldwin, R. M., Seibyl, J. P., Bowers, M., … Laruelle, M. (1998). Increased striatal dopamine transmission in schizophrenia: Confirmation in a second cohort. American Journal of Psychiatry, 155(6), 761–767. https://doi.org/10.1176/ajp.155.6.761

Ahlenius, S. (1999). Clozapine: Dopamine D1receptor agonism in the prefrontal cortex as the code to decipher a Rosetta stone of antipsychotic drugs. Pharmacology and Toxicology, 84(5), 193–196. https://doi.org/10.1111/j.1600-0773.1999.tb01482.x

Alvarez, E., Garcia-Ribera, C., Torrens, M., Udina, C., Guillamat, R., & Casas, M. (1987). Premorbid adjustment scale as a prognostic predictor for schizophrenia. The British Journal of Psychiatry : The Journal of Mental Science, 150, 411. https://doi.org/10.1192/bjp.150.3.411

Andreasen, N. C. (1989). The Scale for the Assessment of Negative Symptoms (SANS): Conceptual and theoretical foundations. The British Journal of Psychiatry Supplement, 155, 49–58. https://doi.org/10.1192/S0007125000291496

Andreasen, N. C., & Olsen, S. (1982). Negative v Positive Schizophrenia: Definition and Validation. Archives of General Psychiatry, 39(7), 789–794. https://doi.org/10.1001/archpsyc.1982.04290070025006

Arseneault, L., Cannon, M., Witton, J., & Murray, R. M. (2004). Causal association between cannabis and psychosis: Examination of the evidence. British Journal of Psychiatry, 184(FEB.), 110–117. https://doi.org/10.1192/bjp.184.2.110

Ascher-Svanum, H., Weiden, P., Nyhuis, A. W., Faries, D. E., Stauffer, V., Kollack-Walker, S., & Kinon, B. J. (2014). Early Perception of Medication Benefit Predicts Subsequent Antipsychotic Response in Schizophrenia. Clinical Schizophrenia & Related Psychoses, 8(2), 84–90A. https://doi.org/10.3371/CSRP.ASWE.022213

Awad, A. G., & Voruganti, L. N. P. (2008). The burden of schizophrenia on caregivers: A review. PharmacoEconomics, 26(2), 149–162. https://doi.org/10.2165/00019053-200826020-00005

Bale, T. L., Baram, T. Z., Brown, A. S., Goldstein, J. M., Insel, T. R., McCarthy, M. M., … Nestler, E. J. (2010). Early life programming and neurodevelopmental disorders. Biological Psychiatry, 68(4), 314–319. https://doi.org/10.1016/j.biopsych.2010.05.028

Barnes, T. R. E. (1989). A rating scale for drug-induced akathisia. British Journal of Psychiatry, 154(MAY), 672–676. https://doi.org/10.1192/bjp.154.5.672

Barnes, T. R. E. (2003). The Barnes Akathisia Rating Scale - Revisited. Journal of Psychopharmacology, 17(4), 365–370. https://doi.org/10.1177/0269881103174013

Berrios, G. E. (1985). Positive and Negative Symptoms and Jackson. Archives of General Psychiatry, 42(1), 95. https://doi.org/10.1001/archpsyc.1985.01790240097011

Birchwood, M. (1992). Early intervention in schizophrenia: Theoretical background and clinical strategies. British Journal of Clinical Psychology, 31(3), 257–278. https://doi.org/10.1111/j.2044-8260.1992.tb00994.x

Brekke, J. S., & Barrio, C. (1997). Cross-ethnic symptom differences in schizophrenia: The influence of culture and minority status. Schizophrenia Bulletin, 23(2), 305–316. https://doi.org/10.1093/schbul/23.2.305

Brown, S., Kim, M., Mitchell, C., & Inskip, H. (2010). Twenty-five year mortality of a community cohort with schizophrenia. British Journal of Psychiatry, 196(2), 116–121. https://doi.org/10.1192/bjp.bp.109.067512

Brunette, M. F., Mueser, K. T., Babbin, S., Meyer-Kalos, P., Rosenheck, R., Correll, C. U., … Kane, J. M. (2018). Demographic and clinical correlates of substance use disorders in first episode psychosis. Schizophrenia Research, 194, 4–12. https://doi.org/10.1016/j.schres.2017.06.039

Buckley, P. F., Miller, B. J., Lehrer, D. S., & Castle, D. J. (2009). Psychiatric comorbidities and schizophrenia. Schizophrenia Bulletin, 35(2), 383–402. https://doi.org/10.1093/schbul/sbn135

Caligiuri, M. P., Lohr, J. B., & Jeste, D. V. (1993). Parkinsonism in neuroleptic-naive schizophrenic patients. In American Journal of Psychiatry. https://doi.org/10.1176/ajp.150.9.1343

Cannon-Spoor, H. E., Potkin, S. G., & Wyatt, R. J. (1982). Measurement of premorbid adjustment in chronic schizophrenia. Schizophrenia Bulletin. https://doi.org/10.1093/schbul/8.3.470

Cannon, M., Caspi, A., Moffitt, T. E., Harrington, H., Taylor, A., Murray, R. M., & Poulton, R. (2002). Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: Results from a longitudinal birth cohort. Archives of General Psychiatry, 59(5), 449–456. https://doi.org/10.1001/archpsyc.59.5.449

Carbon, M., & Correll, C. U. (2014). Clinical predictors of therapeutic response to antipsychotics in schizophrenia. Dialogues in Clinical Neuroscience, 16(4), 505–524.

Carbon, M., Hsieh, C. H., Kane, J. M., & Correll, C. U. (2017). Tardive dyskinesia prevalence in the period of second-generation antipsychotic use: A meta-analysis. Journal of Clinical Psychiatry, 78(3), e264–e278. https://doi.org/10.4088/JCP.16r10832

Carpenter, W. T. (2011). The facts of schizophrenia: A personal commentary. Schizophrenia Research, 128(1–3), 3–4. https://doi.org/10.1016/j.schres.2011.03.002

Carrà, G., Johnson, S., Crocamo, C., Angermeyer, M. C., Brugha, T., Azorin, J. M., … Bebbington, P. E. (2016). Psychosocial functioning, quality of life and clinical correlates of comorbid alcohol and drug dependence syndromes in people with schizophrenia across Europe. Psychiatry Research, 239, 301–307. https://doi.org/10.1016/j.psychres.2016.03.038

Case, M., Stauffer, V. L., Ascher-Svanum, H., Conley, R., Kapur, S., Kane, J. M., … Kinon, B. J. (2011). The heterogeneity of antipsychotic response in the treatment of schizophrenia. Psychological Medicine, 41(6), 1291–1300. https://doi.org/10.1017/S0033291710001893

Caspi, A., & Moffitt, T. E. (2006). Gene-environment interactions in psychiatry: Joining forces with neuroscience. Nature Reviews Neuroscience, 7(7), 583–590. https://doi.org/10.1038/nrn1925

Cassady, S. L., Adami, H., Moran, M., Kunkel, R., & Thaker, G. K. (1998). Spontaneous dyskinesia in subjects with schizophrenia spectrum personality. American Journal of Psychiatry, 155(1), 70–75. https://doi.org/10.1176/ajp.155.1.70

Chakos, M. H., Alvir, J. M. J., Woerner, M. G., Koreen, A., Geisler, S., Mayerhoff, D., … Lieberman, J. A. (1996). Incidence and correlates of tardive dyskinesia in first episode of schizophrenia. Archives of General Psychiatry. https://doi.org/10.1001/archpsyc.1996.01830040049009

Chatterjee, A., Chakos, M., Koreen, A., Geisler, S., Sheitman, B., Woerner, M., … Lieberman, J. A. (1995). Prevalence and clinical correlates of extrapyramidal signs and spontaneous dyskinesia in never-medicated schizophrenic patients. American Journal of Psychiatry, 152(12), 1724–1729. https://doi.org/10.1176/ajp.152.12.1724

Chen, L., Ascher-Svanum, H., Lawson, A., Stauffer, V. L., Nyhuis, A., Haynes, V., … Kinon, B. J. (2013). Movement disorder profile and treatment outcomes in a one-year study of patients with schizophrenia. Neuropsychiatric Disease and Treatment, 9, 815–822. https://doi.org/10.2147/NDT.S43574

Correll, C. U., Malhotra, A. K., Kaushik, S., McMeniman, M., & Kane, J. M. (2003). Early prediction of antipsychotic response in schizophrenia. American Journal of Psychiatry. https://doi.org/10.1176/appi.ajp.160.11.2063

Correll, C. U., & Schenk, E. M. (2008). Tardive dyskinesia and new antipsychotics. Current Opinion in Psychiatry, 21(2), 151–156. https://doi.org/10.1097/YCO.0b013e3282f53132

Cortese, L., Caligiuri, M. P., Malla, A. K., Manchanda, R., Takhar, J., & Haricharan, R. (2005). Relationship of neuromotor disturbances to psychosis symptoms in first-episode neuroleptic-naïve schizophrenia patients. Schizophrenia Research, 75(1), 65–75. https://doi.org/10.1016/j.schres.2004.08.003

Crow, T. J. (1980). Molecular pathology of schizophrenia: More than one disease process? British Medical Journal, 280(6207), 66–68. https://doi.org/10.1136/bmj.280.6207.66

Crump, C., Winkleby, M. A., Sundquist, K., & Sundquist, J. (2013). Comorbidities and mortality in persons with schizophrenia: A Swedish national cohort study. American Journal of Psychiatry, 170(3), 324–333. https://doi.org/10.1176/appi.ajp.2012.12050599

Daskalakis, Z. J., Christensen, B. K., Fitzgerald, P. B., & Chen, R. (2008). Dysfunctional neural plasticity in patients with schizophrenia. Archives of General Psychiatry. https://doi.org/10.1001/archpsyc.65.4.378

De Girolamo, G., Dagani, J., Purcell, R., Cocchi, A., & McGorry, P. D. (2012). Age of onset of mental disorders and use of mental health services: Needs, opportunities and obstacles. Epidemiology and Psychiatric Sciences, 21(1), 47–57. https://doi.org/10.1017/S2045796011000746

De Haan, L., Van Bruggen, M., Lavalaye, J., Booij, J., Dingemans, P. M. A. J., & Linszen, D. (2003). Subjective experience and D 2 receptor occupancy in patients with recent-onset schizophrenia treated with low-dose olanzapine or haloperidol: A randomized, double-blind study. American Journal of Psychiatry, 160(2), 303–309. https://doi.org/10.1176/appi.ajp.160.2.303

Derks, E. M., Fleischhacker, W. W., Boter, H., Peuskens, J., & Kahn, R. S. (2010). Antipsychotic drug treatment in first-episode psychosis should patients be switched to a different antipsychotic drug after 2, 4, or 6 weeks of nonresponse? Journal of Clinical Psychopharmacology, 30(2), 176–180. https://doi.org/10.1097/JCP.0b013e3181d2193c

Díaz, I., Pelayo-Terán, J. M., Pérez-Iglesias, R., Mata, I., Tabarés-Seisdedos, R., Suárez-Pinilla, P., … Crespo-Facorro, B. (2013). Predictors of clinical remission following a first episode of non-affective psychosis: sociodemographics, premorbid and clinical variables. Psychiatry Research, 206(2–3), 181–187. https://doi.org/10.1016/j.psychres.2012.10.011

Eugene, A. R., & Masiak, J. (2017). A pharmacodynamic modelling and simulation study identifying gender differences of daily olanzapine dose and dopamine D2-receptor occupancy. Nordic Journal of Psychiatry, 71(6), 417–424. https://doi.org/10.1080/08039488.2017.1314011

Farde, L., Nordström, a L., Wiesel, F. a, Pauli, S., Halldin, C., & Sedvall, G. (1992). Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. Archives of General Psychiatry, 49(7), 538–544. https://doi.org/10.1001/archpsyc.1992.01820070032005

Fenton, W. S. (2000). Prevalence of spontaneous dyskinesia in schizophrenia. Journal of Clinical Psychiatry, 61(SUPPL. 4), 10–14.

Fenton, W. S., Wyatt, R. J., & McGlashan, T. H. (1994). Risk Factors for Spontaneous Dyskinesia in Schizophrenia. Archives of General Psychiatry, 51(8), 643–650. https://doi.org/10.1001/archpsyc.1994.03950080055008

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, W. J. B. (2002). Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition. (SCID-I/P). New York: Biometrics Research, NYSPI.

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rössler, A., Schultze-Lutter, F., … Yung, A. (2013). The psychosis high-risk state: A comprehensive state-of-the-art review. Archives of General Psychiatry, 70(1), 107–120. https://doi.org/10.1001/jamapsychiatry.2013.269

Fusar-Poli, P., & Meyer-Lindenberg, A. (2013). Striatal presynaptic dopamine in schizophrenia, part II: Meta-analysis of [18F/11C]-DOPA PET studies. Schizophrenia Bulletin, 39(1), 33–42. https://doi.org/10.1093/schbul/sbr180

Fusar-Poli, P., Perez, J., Broome, M., Borgwardt, S., Placentino, A., Caverzasi, E., … McGuire, P. (2007). Neurofunctional correlates of vulnerability to psychosis: A systematic review and meta-analysis. Neuroscience and Biobehavioral Reviews, 31(4), 465–484. https://doi.org/10.1016/j.neubiorev.2006.11.006

Gaebel, W., Riesbeck, M., Wölwer, W., Klimke, A., Eickhoff, M., von Wilmsdorff, M., … Möller, H. J. (2014). Rates and predictors of remission in first-episode

schizophrenia within 1year of antipsychotic maintenance treatment. Results of a randomized controlled trial within the German Research Network on Schizophrenia. Schizophrenia Research, 152(2–3), 478–486. https://doi.org/10.1016/j.schres.2013.04.012

Garcia-Ribera, C. (1986). Tardive Dyskinesia and Parkinsonism. British Journal of Psychiatry, 149, 665–666. https://doi.org/10.1192/S0007125000140401

García-Ribera, C., & Bulbena, A. (2011). Determinants of medicine-taking in psychiatric patients. Current Clinical Pharmacology, 6(2), 100–107. https://doi.org/http://dx.doi.org/10.2174/157488411796151156

Garcia-Ribera, C., & Ruiz Ripoll, A. I. (2010). Antipsicoticos. In J. Vallejo & C. Leal (Eds.), Tratado de Psiquiatria (pp. 2113–2135). Barcelona: Ars Medica.

Garcia-Ribera, C., Ruiz Ripoll, A. I., & Vidal Guitart, X. (1991). Tardive Dyskinesia in a spanish inpatient population. Biological Psychiatry, 29(11s), 670s.

Garcia-Rizo, C., Fernandez-Egea, E., Oliveira, C., Justicia, A., Parellada, E., Bernardo, M., & Kirkpatrick, B. (2012). Prolactin concentrations in newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis. Schizophrenia Research, 134(1), 16–19. https://doi.org/10.1016/j.schres.2011.07.025

Garver, D. L., Holcomb, J. A., & Christensen, J. D. (2000). Heterogeneity of response to antipsychotics from multiple disorders in the schizophrenia spectrum. Journal of Clinical Psychiatry. https://doi.org/10.4088/JCP.v61n1213

Gerlach, J. (1979). Tardive Dyskinesia. Dan Med. Bull., 46, 209–245.

Gerlach, J., & Garcia Ribera, C. (1996). De los modelos en animales a los efectos clínicos. In C. Garcia Ribera (Ed.), Nuevos Antipsicóticos Atípicos. Barcelona: Masson.

Gervin, M., Browne, S., Lane, A., Clarke, M., Waddington, J. L., Larkin, C., & O'Callaghan, E. (1998). Spontaneous abnormal involuntary movements in first-episode schizophrenia and schizophreniform disorder: Baseline rate in a group of patients from an irish catchment area. American Journal of Psychiatry, 155(9), 1202–1206. https://doi.org/10.1176/ajp.155.9.1202

Glazer, W. M. (2000). Expected incidence of tardive dyskinesia associated with atypical antipsychotics. Journal of Clinical Psychiatry, 61(SUPPL. 4), 21–26.

Goldberg, T. E., Burdick, K. E., McCormack, J., Napolitano, B., Patel, R. C., Sevy, S. M., … Robinson, D. G. (2009). Lack of an inverse relationship between duration of untreated psychosis and cognitive function in first episode schizophrenia. Schizophrenia Research, 107(2–3), 262–266. https://doi.org/10.1016/j.schres.2008.11.003

Green, M. F., Nuechterlein, K. H., Gold, J. M., Barch, D. M., Cohen, J., Essock, S., … Marder, S. R. (2004). Approaching a consensus cognitive battery for clinical trials in schizophrenia: The NIMH-MATRICS conference to select cognitive domains and test criteria. Biological Psychiatry. https://doi.org/10.1016/j.biopsych.2004.06.023

Gureje, O., & Bamidele, R. W. (1998). Gender and schizophrenia: Association of age at onset with antecedent, clinical and outcome features. Australian and New Zealand Journal of Psychiatry, 32(3), 415–423. https://doi.org/10.3109/00048679809065536

Guy, W. (1976). ECDEU Assessment Manual for Psychopharmacology. (W. Guy, Ed.). Rockville, MD: US Department of Heath, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration.

Hafner, H., an der Heiden, W., Behrens, S., Gattaz, W. F., Hambrecht, M., Loffler, W., … Stein, A. (1998). Causes and Consequences of the Gender Difference in Age at Onset of Schizophrenia. Schizophrenia Bulletin, 24(1), 99–113. https://doi.org/10.1093/oxfordjournals.schbul.a033317

Hamera, E. K., Peterson, K. A., Young, L. M., & Schaumloffel, M. M. N. (1992). Symptom monitoring in schizophrenia: Potential for enhancing self-care. Archives of Psychiatric Nursing, 6(6), 324–330. https://doi.org/10.1016/0883-9417(92)90084-V

Hansen, T. E., Glazer, W. M., & Moore, D. C. (1986). Tremor and tardive dyskinesia. Journal of Clinical Psychiatry, 47(9), 461–464.

Harding, C. M., Zubin, J., & Strauss, J. S. (1992). Chronicity in schizophrenia: Revisited. British Journal of Psychiatry, 161(OCT. SUPPL. 18), 27–37.

Harrison, G., Hopper, K., Craig, T., Laska, E., Siegel, C., Wanderling, J., … Wiersma, D. (2001). Recovery from psychotic illness: A 15- and 25-year international follow-up study. British Journal of Psychiatry, 178(JUNE), 506–517. https://doi.org/10.1192/bjp.178.6.506

Hollingshead, A. B. (1957). Two factor index of social position. (Y. University, Ed.). New Haven, CT: Mimeo.

Hollingshead, A. B. (1971). Commentary on "The Indiscriminate State of Social Class Measurement." Social Forces, 49(4), 563. https://doi.org/10.2307/2576737

Honer, W. G., Kopala, L. C., & Rabinowitz, J. (2005). Extrapyramidal symptoms and signs in first-episode, antipsychotic exposed and non-exposed patients with schizophrenia or related psychotic illness. Journal of Psychopharmacology, 19(3), 277–285. https://doi.org/10.1177/0269881105051539

Horga, G., Cassidy, C. M., Xu, X., Moore, H., Slifstein, M., Van Snellenberg, J. X., & Abi-Dargham, A. (2016). Dopamine-related disruption of functional topography of striatal connections in unmedicated patients with schizophrenia. JAMA Psychiatry, 73(8), 862–870. https://doi.org/10.1001/jamapsychiatry.2016.0178

Howes, O. D., Kambeitz, J., Kim, E., Stahl, D., Slifstein, M., Abi-Dargham, A., & Kapur, S. (2012). The nature of dopamine dysfunction in schizophrenia and what this means for treatment: Meta-analysisof imaging studies. Archives of General Psychiatry, 69(8), 776–786. https://doi.org/10.1001/archgenpsychiatry.2012.169

Howes, O. D., & Kapur, S. (2009). The dopamine hypothesis of schizophrenia: Version III - The final common pathway. Schizophrenia Bulletin, 35(3), 549–562. https://doi.org/10.1093/schbul/sbp006

Howes, O. D., Mccutcheon, R., Owen, M. J., Murray, P. R., & Studies, P. (2017). The role of genes, stress and dopamine in the development of schizophrenia Europe PMC Funders Group, 81(1), 9–20. https://doi.org/10.1016/j.biopsych.2016.07.014

Jablensky, A., Sartorius, N., Ernberg, G., Anker, M., Korten, A., Cooper, J. E., … Bertelsen, A. (1992). Schizophrenia: manifestations, incidence and course in different cultures A World Health Organization Ten-Country Study. Psychological Medicine. Monograph Supplement, 20, 1. https://doi.org/10.1017/S0264180100000904

Janno, S., Holi, M. M., Tuisku, K., & Wahlbeck, K. (2005). Validity of Simpson-Angus Scale (SAS) in a naturalistic schizophrenia population. BMC Neurology. https://doi.org/10.1186/1471-2377-5-5

Jibson, M. D., & Tandon, R. (1998). New atypical antipsychotic medications. Journal of Psychiatric Research, 32(3–4), 215–228. https://doi.org/10.1016/S0022-3956(98)00023-5

Jones, P. B., & Buckley, P. F. (2006). Schizophrenia. Elsevier Ltd.

Kane, J., Honigfeld, G., Singer, J., & Meltzer, H. (1988). Clozapine for the Treatment-Resistant Schizophrenic: A Double-blind Comparison With Chlorpromazine. Archives of General Psychiatry. https://doi.org/10.1001/archpsyc.1988.01800330013001

Kane, J. M. (2004). Tardive dyskinesia rates with atypical antipsychotics in adults: Prevalence and incidence. Journal of Clinical Psychiatry, 65(SUPPL. 9), 16–20.

Kane, J. M., & Garcia-Ribera, C. (2009). Clinical guideline recommendations for antipsychotic long-acting injections. British Journal of Psychiatry, 195(SUPPL. 52). https://doi.org/10.1192/bjp.195.52.s63

Kane, J. M., Woerner, M., Borenstein, M., Wegner, J., & Lieberman, J. (1986). Integrating incidence and prevalence of tardive dyskinesia. Psychopharmacology Bulletin, 22(1), 254–258. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2873613

Kane, J. M., Woerner, M., & Lieberman, J. (1988). Tardive dyskinesia: prevalence, incidence, and risk factors. Journal of Clinical Psychopharmacology.

Kaplan, H., Sadock, B., & Grebb, Jar. (1994). Schizophrenia. In R. D (Ed.), Kaplan and Sadock's Synopsis of Psychiatry (seventh). Baltimore,USA.

Kapur, S. (2011). What Kraepelin might say about schizophrenia: Just the facts. Schizophrenia Research, 128(1–3), 1–2. https://doi.org/10.1016/j.schres.2011.02.012

Kapur, S., & Seeman, P. (2001). Does fast dissociation from the dopamine D2 receptor explain the action of atypical antipsychotics?: A new hypothesis. American Journal of Psychiatry, 158(3), 360–369. https://doi.org/10.1176/appi.ajp.158.3.360

Kapur, S., Zipursky, R., Jones, C., Remington, G., & Houle, S. (2000). Relationship Between Dopamine D 2 Occupancy, Clinical Response, and Side Effects: A Double-Blind PET Study of First-Episode Schizophrenia. American Journal of Psychiatry, 157(April), 514–520. https://doi.org/10.1176/appi.ajp.157.4.514

Kavanagh, D. H., Tansey, K. E., O'Donovan, M. C., & Owen, M. J. (2015). Schizophrenia genetics: Emerging themes for a complex disorder. Molecular Psychiatry, 20(1), 72–76. https://doi.org/10.1038/mp.2014.148

Kay, S. R., Opler, L. A., & Lindenmayer, J. P. (1988). Reliability and validity of the positive and negative syndrome scale for schizophrenics. Psychiatry Research. https://doi.org/10.1016/0165-1781(88)90038-8

Keefe, R., & Harvey, P. (2012). Cognitive impairment in schizophrenia. Handbook of Experimental Pharmacology, (213), 11–37. https://doi.org/10.1007/978-3-642-25758-2_2

Kendler, K. S., & Gardner, C. O. (1997). The risk for psychiatric disorders in relatives of schizophrenic and control probands: a comparison of three independent studies. Psychological Medicine, 27(2), 411–419. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9089833

Kendler, K. S., McGuire, M., Gruenberg, A. M., O'Hare, A., Spellman, M., & Walsh, D. (1993). The Roscommon Family Study: I. Methods, Diagnosis of Probands, and Risk of Schizophrenia in Relatives. Archives of General Psychiatry, 50(7), 527–540. https://doi.org/10.1001/archpsyc.1993.01820190029004

Keshavan, M. S., Tandon, R., Boutros, N. N., & Nasrallah, H. A. (2008). Schizophrenia, "just the facts": What we know in 2008. Part 3: Neurobiology. Schizophrenia Research, 106(2–3), 89–107. https://doi.org/10.1016/j.schres.2008.07.020

Kessler R, McGonagle K, Z. S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry, 51(1), 8–19.

Kety, S. S., Rosenthal, D., Wender, P. H., & Schulsinger, F. (1971). Mental illness in the biological and adoptive families of adpoted schizophrenics. The American Journal of Psychiatry, 128(3), 302–306. https://doi.org/10.1176/ajp.128.3.302

Kinon, B. J., Kane, J. M., Chakos, M., & Munne, R. (1993). Possible predictors of neuroleptic-resistant schizophrenic relapse: influence of negative symptoms and acute extrapyramidal side effects. Psychopharmacology Bulletin.

Kinon, B. J., Kane, J. M., Johns, C., Perovich, R., Ismi, M., Koreen, A., & Weiden, P. (1993). Treatment of neuroleptic-resistant schizophrenic relapse. Psychopharmacology Bulletin.

Knapp, M., Mangalore, R., & Simon, J. (2004). The global costs of Schizophrenia. Schizophrenia Bulletin, 30(2), 279–293. https://doi.org/10.1093/oxfordjournals.schbul.a007078

Koreen, A. R., Siris, S. G., Chakos, M., Alvir, J., Mayerhoff, D., & Lieberman, J. (1993). Depression in first-episode schizophrenia. American Journal of Psychiatry, 150(11), 1643–1648. https://doi.org/10.1176/ajp.150.11.1643

Kuroki, T., Nagao, N., & Nakahara, T. (2008). Neuropharmacology of second-generation antipsychotic drugs: a validity of the serotonin-dopamine hypothesis. Progress in Brain Research, 172, 199–212. https://doi.org/10.1016/S0079-6123(08)00910-2

Larsen, T. K., McGlashan, T. H., Johannessen, J. O., & Vlbe-Hansen, L. (1996). First-episode schizophrenia: II. Premorbid patterns by gender. Schizophrenia Bulletin, 22(2), 257–269. https://doi.org/10.1093/schbul/22.2.257

Larsen, T. K., Melle, I., Auestad, B., Friis, S., Haahr, U., Johannessen, J. O., … McGlashan, T. H. (2006). Substance abuse in first-episode non-affective psychosis. Schizophrenia Research, 88(1–3), 55–62. https://doi.org/10.1016/j.schres.2006.07.018

Laruelle, M., Abi-Dargham, A., Gil, R., Kegeles, L., & Innis, R. (1999). Increased dopamine transmission in schizophrenia: relationship to illness phases. Biological Psychiatry, 46(1), 56–72. https://doi.org/10.1016/S0006-3223(99)00067-0

Lauterbach, E. C., Carter, W. G., Rathke, K. M., Thomas, B. H., Shillcutt, S. D., Vogel, R. L., … Nelson, W. H. (2001). Tardive dyskinesia--diagnostic issues, subsyndromes, and concurrent movement disorders: a study of state hospital inpatients referred to a movement disorder consultation service. Schizophr Bull, 27(4), 601–613. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11824487

Lederbogen, F., Kirsch, P., Haddad, L., Streit, F., Tost, H., Schuch, P., … Meyer-Lindenberg, A. (2011). City living and urban upbringing affect neural social stress processing in humans. Nature, 474(7352), 498–501. https://doi.org/10.1038/nature10190

Lee, J., Poon, L. Y., & Chong, S. A. (2008). Spontaneous Dyskinesia in first-episode psychosis in a southeast Asian population. Journal of Clinical Psychopharmacology, 28(5), 536–539. https://doi.org/10.1097/JCP.0b013e3181845f59

Lee, S. H., Decandia, T. R., Ripke, S., Yang, J., Sullivan, P. F., Goddard, M. E., … Wray, N. R. (2012). Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs. Nature Genetics, 44(3), 247–250. https://doi.org/10.1038/ng.1108

Leucht, S., Tardy, M., Komossa, K., Heres, S., Kissling, W., Salanti, G., & Davis, J. M. (2012). Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: A systematic review and meta-analysis. The Lancet. https://doi.org/10.1016/S0140-6736(12)60239-6

Leucht, S., & Zhao, J. (2014). Early improvement as a predictor of treatment response and remission in patients with schizophrenia: A pooled, post-hoc analysis from the asenapine development program. Journal of Psychopharmacology, 28(4), 387–394. https://doi.org/10.1177/0269881113517956

Levine, S. Z., Rabinowitz, J., Uher, R., & Kapur, S. (2015). Biomarkers of treatment outcome in schizophrenia: Defining a benchmark for clinical significance.

European Neuropsychopharmacology, 25(10), 1578–1585. https://doi.org/10.1016/j.euroneuro.2015.06.008

Levinson, D. F., Simpson, G. M., Singh, H., Yadalam, K., Jain, a, Stephanos, M. J., & Silver, P. (1990). Fluphenazine dose, clinical response, and extrapyramidal symptoms during acute treatment. Archives of General Psychiatry.

Lewis, G., David, A., Andréassson, S., & Allebeck, P. (1992). Schizophrenia and city life. The Lancet, 340(8812), 137–140. https://doi.org/10.1016/0140-6736(92)93213-7

Lieberman, J. A., Koreen, A. R., Chakos, M., Sheitman, B., Woerner, M., Alvir, J. M. J., & Bilder, R. (1996). Factors influencing treatment response and outcome of first-episode schizophrenia: Implications for understanding the pathophysiology of schizophrenia. Journal of Clinical Psychiatry, 57(SUPPL. 9), 5–9.

Lieberman, J., Jody, D., Geisler, S., Alvir, J., Loebel, A., Szymanski, S., … Borenstein, M. (1993). Time course and biologic correlates of treatment response in first-episode schizophrenia. Archives of General Psychiatry. https://doi.org/10.1001/archpsyc.1993.01820170047006.Objective

Lohr, J. (2005). Is Tardive Dyskinesia disappearing? In W. Factor, Lang (Ed.), Drug-induced Movement Disorders (second ed.). Malden, MS: Blackwell-Futura.

Marsden, C. D., Tarsy, D., & Baldessarini, R. (1975). Spontaneous and Drug-induced movement disorders in psychotic patients. In Benson & Bluner (Eds.), Psychiatric Aspects of Neurologic Disease (pp. 219–266). New York: Stratton, Grune &.

Marshall, M., Lewis, S., Lockwood, A., Drake, R., Jones, P., & Croudace, T. (2005). Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: A systematic review. Archives of General Psychiatry, 62(9), 975–983. https://doi.org/10.1001/archpsyc.62.9.975

McCreadie, R. G., Srinivasan, T. N., Padmavati, R., & Thara, R. (2005). Extrapyramidal symptoms in unmedicated schizophrenia. Journal of Psychiatric Research, 39(3), 261–266. https://doi.org/10.1016/j.jpsychires.2004.08.002

McGorry, P. (2011). Transition to adulthood: The critical period for pre-emptive, disease-modifying care for schizophrenia and related disorders. Schizophrenia Bulletin, 37(3), 524–530. https://doi.org/10.1093/schbul/sbr027

McGorry, P. D. (2002). The recognition and optimal management of early psychosis: an evidence-based reform. World Psychiatry : Official Journal of the World Psychiatric Association (WPA), 1(2), 76–83. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1489880&tool=pmcentrez&rendertype=abstract

McGowan, PO; Sasaki, A; D'Alessio, AC; Dymov, S; Labonté, B; Szyf, M. E. A. . (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci., 12, 342–348.

McGrath, J., Saha, S., Welham, J., El Saadi, O., MacCauley, C., & Chant, D. (2004). A systematic review of the incidence of schizophrenia: The distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Medicine, 2. https://doi.org/10.1186/1741-7015-2-13

Melle, I., Johannessen, J. O., Friis, S., Haahr, U., Joa, I., Larsen, T. K., … McGlashan, T. H. (2006). Early detection of the first episode of schizophrenia and suicidal behavior. American Journal of Psychiatry, 163(5), 800–804. https://doi.org/10.1176/appi.ajp.163.5.800

Meltzer, H. Y., & Huang, M. (2008). In vivo actions of atypical antipsychotic drug on serotonergic and dopaminergic systems. Progress in Brain Research, 172, 177–197. https://doi.org/10.1016/S0079-6123(08)00909-6

Meltzer, H. Y., & Massey, B. W. (2011). The role of serotonin receptors in the action of atypical antipsychotic drugs. Current Opinion in Pharmacology, 11(1), 59–67. https://doi.org/10.1016/j.coph.2011.02.007

Meng, H., Schimmelmann, B. G., Mohler, B., Lambert, M., Branik, E., Koch, E., … Bürgin, D. (2006). Pretreatment social functioning predicts 1-year outcome in early onset psychosis. Acta Psychiatrica Scandinavica, 114(4), 249–256. https://doi.org/10.1111/j.1600-0447.2006.00773.x

Messias, E. L., Chen, C. Y., & Eaton, W. W. (2007). Epidemiology of Schizophrenia: Review of Findings and Myths. Psychiatric Clinics of North America, 30(3), 323–338. https://doi.org/10.1016/j.psc.2007.04.007

Miller, D. D., Caroff, S. N., Davis, S. M., Rosenheck, R. A., McEvoy, J. P., Saltz, B. L., … Lieberman, J. A. (2008). Extrapyramidal side-effects of antipsychotics in a randomised trial. British Journal of Psychiatry, 193(4), 279–288. https://doi.org/10.1192/bjp.bp.108.050088

Mittal, V. A., Neumann, C., Saczawa, M., & Walker, E. F. (2008). Longitudinal progression of movement abnormalities in relation to psychotic symptoms in adolescents at high risk of schizophrenia. Archives of General Psychiatry, 65(2), 165–171. https://doi.org/10.1001/archgenpsychiatry.2007.23

Mittal, V. A., Orr, J. M., Turner, J. A., Pelletier, A. L., Dean, D. J., Lunsford-Avery, J., & Gupta, T. (2013). Striatal abnormalities and spontaneous dyskinesias in non-clinical psychosis. Schizophrenia Research, 151(1–3), 141–147. https://doi.org/10.1016/j.schres.2013.10.003

Mittal, V. A., & Walker, E. F. (2007). Movement abnormalities predict conversion to Axis I psychosis among prodromal adolescents. Journal of Abnormal Psychology, 116(4), 796–803. https://doi.org/10.1037/0021-843X.116.4.796

Mizrahi, R., Rusjan, P., Agid, O., Graff, A., Mamo, D. C., Zipursky, R. B., & Kapur, S. (2007). Adverse subjective experience with antipsychotics and its relationship to striatal and extrastriatal D2receptors: A PET study in schizophrenia. American Journal of Psychiatry, 164(4), 630–637. https://doi.org/10.1176/ajp.2007.164.4.630

Moffitt, T. E., Caspi, A., & Rutter, M. (2005). Strategy for investigating interactions between measured genes and measured environments. Archives of General Psychiatry, 62(5), 473–481. https://doi.org/10.1001/archpsyc.62.5.473

Nordström, A. L., Farde, L., Wiesel, F. A., Forslund, K., Pauli, S., Halldin, C., & Uppfeldt, G. (1993). Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: A double-blind PET study of schizophrenic patients. Biological Psychiatry, 33(4), 227–235. https://doi.org/10.1016/0006-3223(93)90288-O

Nuechterlein, K. H., Dawson, M. E., Ventura, J., Gitlin, M., Subotnik, K. L., Snyder, K. S., … Bartzokis, G. (1994). The vulnerability/stress model of schizophrenic relapse: a longitudinal study. Acta Psychiatrica Scandinavica, 89, 58–64. https://doi.org/10.1111/j.1600-0447.1994.tb05867.x

Oakley, P., Kisely, S., Baxter, A., Harris, M., Desoe, J., Dziouba, A., & Siskind, D. (2018). Increased mortality among people with schizophrenia and other non-affective psychotic disorders in the community: A systematic review and meta-analysis. Journal of Psychiatric Research, 102, 245–253. https://doi.org/10.1016/j.jpsychires.2018.04.019

Oosthuizen, P. P., Emsley, R. A., Maritz, J. S., Turner, J. A., & Keyter, N. (2003). Incidence of tardive dyskinesia in first-episode psychosis patients treated with low-dose haloperidol. Journal of Clinical Psychiatry, 64(9), 1075–1080. https://doi.org/10.4088/JCP.v64n0913

Owens, D. G. C. (2014). A Guide to the Extrapyramidal Side-Effects of Antipsychotic. (Cambridge University Press, Ed.), The Journal of Clinical Psychiatry (Vol. 61). Cambridge, UK. https://doi.org/10.4088/JCP.v61n1112e

Owens, D. G. C., Johnstone, E. C., & Frith, C. D. (1982). Spontaneous Involuntary Disorders of Movement: Their Prevalence, Severity, and Distribution in Chronic Schizophrenics with and without Treatment with Neuroleptics. Archives of General Psychiatry, 39(4), 452–461. https://doi.org/10.1001/archpsyc.1982.04290040052008

Palacios, J., & Mengod, G. (1996). Selectividad regional de los antipsicóticos atípicos. In C. Garcia Ribera (Ed.), Nuevos Antipsicóticos Atípicos. Barcelona: Masson.

Palmer, B. A., Pankratz, V. S., & Bostwick, J. M. (2005). The lifetime risk of suicide in schizophrenia: A reexamination. Archives of General Psychiatry, 62(3), 247–253. https://doi.org/10.1001/archpsyc.62.3.247

Pappa, S., & Dazzan, P. (2009). Spontaneous movement disorders in antipsychotic-naive patients with first-episode psychoses: A systematic review. Psychological Medicine, 39(7), 1065–1076. https://doi.org/10.1017/S0033291708004716

Parellada, E., Velligan, D., Emsley, R., & Kissling, W. (2012). Long-acting injectable antipsychotics in first-episode schizophrenia. Schizophrenia Research and Treatment.

Pearce, J., & Clough, C. (1986). Drug-induced movement disorders. In N. Shah & A. Donald (Eds.), Movement Disorders (pp. 343–364). New York: Plenum Publishing Corp.

Peen, J., Schoevers, R. A., Beekman, A. T., & Dekker, J. (2010). The current status of urban-rural differences in psychiatric disorders. Acta Psychiatrica Scandinavica, 121(2), 84–93. https://doi.org/10.1111/j.1600-0447.2009.01438.x

Peluso, M. J., Lewis, S. W., Barnes, T. R. E., & Jones, P. B. (2012). Extrapyramidal motor side-effects of firstand second-generation antipsychotic drugs. British Journal of Psychiatry, 200(5), 387–392. https://doi.org/10.1192/bjp.bp.111.101485

Perkins, D. O., Gu, H., Boteva, K., & Lieberman, J. A. (2005). Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: A critical review and meta-analysis. American Journal of Psychiatry, 162(10), 1785–1804. https://doi.org/10.1176/appi.ajp.162.10.1785

Petruzzelli, M. G., Margari, M., Peschechera, A., de Giambattista, C., De Giacomo, A., Matera, E., & Margari, F. (2018). Hyperprolactinemia and insulin resistance in drug naive patients with early onset first episode psychosis. BMC Psychiatry, 18(1), 246. https://doi.org/10.1186/s12888-018-1827-3

Post, R. M., & Goodwin, F. K. (1975). Time-dependent effects of phenothiazines on dopamine turnover in psychiatric patients. Science, 190(4213), 488–489. https://doi.org/10.1126/science.1166321

Poulton, R., Caspi, A., Moffitt, T. E., Cannon, M., Murray, R., & Harrington, H. (2000). Children's self-reported psychotic symptoms and adult schizophreniform disorder: A 15-year longitudinal study. Archives of General Psychiatry, 57(11), 1053–1058. https://doi.org/10.1001/archpsyc.57.11.1053

Rabinowitz, J., Harvey, P. D., Eerdekens, M., & Davidson, M. (2006). Premorbid functioning and treatment response in recent-onset schizophrenia. British Journal of Psychiatry, 189(JULY), 31–35. https://doi.org/10.1192/bjp.bp.105.013276

Rabinowitz, J., Werbeloff, N., Caers, I., Mandel, F. S., Stauffer, V., Ménard, F., … Kapur, S. (2014). Determinants of antipsychotic response in schizophrenia: Implications for practice and future clinical trials. Journal of Clinical Psychiatry, 75(4). https://doi.org/10.4088/JCP.13m08853

Rapoport, J. L., Giedd, J. N., & Gogtay, N. (2012). Neurodevelopmental model of schizophrenia: Update 2012. Molecular Psychiatry, 17(12), 1228–1238. https://doi.org/10.1038/mp.2012.23

Regier, D. A., Farmer, M. E., Rae, D. S., Locke, B. Z., Keith, S. J., Judd, L. L., & Goodwin, F. K. (1990). Comorbidity of Mental Disorders With Alcohol and Other Drug Abuse: Results From the Epidemiologic Catchment Area (ECA) Study. JAMA: The Journal of the American Medical Association, 264(19), 2511–2518. https://doi.org/10.1001/jama.1990.03450190043026

Remington, G., Foussias, G., Agid, O., Fervaha, G., Takeuchi, H., & Hahn, M. (2014). The neurobiology of relapse in schizophrenia. Schizophrenia Research, 152(2–3), 381–390. https://doi.org/10.1016/j.schres.2013.10.009

Riecher-Rössler, A., Rybakowski, J. K., Pflueger, M. O., Beyrau, R., Kahn, R. S., Malik, P., & Fleischhacker, W. W. (2013). Hyperprolactinemia in antipsychotic-naive patients with first-episode psychosis. Psychological Medicine, 43(12), 2571–2582. https://doi.org/10.1017/S0033291713000226

Ripke, S., Neale, B. M., Corvin, A., Walters, J. T. R., Farh, K. H., Holmans, P. A., … O'Donovan, M. C. (2014). Biological insights from 108 schizophrenia-associated genetic loci. Nature, 511(7510), 421–427. https://doi.org/10.1038/nature13595

Robinson, D. G., Woerner, M. G., Alvir, J. M., Geisler, S., Koreen, a, Sheitman, B., … Lieberman, J. a. (1999). Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. The American Journal of Psychiatry. https://doi.org/10.1176/ajp.156.4.544

Robinson, D. G., Woerner, M. G., Napolitano, B., Patel, R. C., Sevy, S. M., Gunduz-Bruce, H., … Kane, J. M. (2006). Randomized comparison of olanzapine versus risperidone for the treatment of first-episode schizophrenia: 4-Month outcomes.

American Journal of Psychiatry, 163(12), 2096–2102. https://doi.org/10.1176/ajp.2006.163.12.2096

Robinson, D., Woerner, M., & Schooler, N. (2000). Intervention research in psychosis: Issues related to clinical assessment. Schizophrenia Bulletin, 26(3), 551–556. https://doi.org/10.1093/oxfordjournals.schbul.a033476

Rund, B. R. (2014). Does active psychosis cause neurobiological pathology? A critical review of the neurotoxicity hypothesis. Psychological Medicine, 44(8), 1577–1590. https://doi.org/10.1017/S0033291713002341

Rurhmann, Ruhrmann, S., Schultze-Lutter, F., Salokangas, R. K. R., Heinimaa, M., Linszen, D., … Klosterkötter, J. (2010). Prediction of Psychosis in Adolescents and Young Adults at High Risk. Archives of General Psychiatry. https://doi.org/10.1001/archgenpsychiatry.2009.206

Samara, M. T., Leucht, C., Leeflang, M. M., Anghelescu, I. G., Chung, Y. C., Crespo-Facorro, B., … Leucht, S. (2015). Early Improvement As a Predictor of Later Response to Antipsychotics in Schizophrenia: A Diagnostic Test Review. The American Journal of Psychiatry, 172(7), 617–629. https://doi.org/10.1176/appi.ajp.2015.14101329

Schneider-Thoma, J., Efthimiou, O., Huhn, M., Krause, M., Reichelt, L., Röder, H., … Leucht, S. (2018). Second-generation antipsychotic drugs and short-term mortality: a systematic review and meta-analysis of placebo-controlled randomised controlled trials. The Lancet Psychiatry. https://doi.org/10.1016/S2215-0366(18)30177-9

Schooler, N. R., & Kane, J. M. (1982). Research Diagnoses for Tardive Dyskinesia. Archives of General Psychiatry. https://doi.org/10.1001/archpsyc.1982.04290040080014

Schooler, N., Rabinowitz, J., Davidson, M., Emsley, R., Harvey, P. D., Kopala, L., … De Smedt, G. (2005). Risperidone and haloperidol in first-episode psychosis: A long-term randomized trial. American Journal of Psychiatry, 162(5), 947–953. https://doi.org/10.1176/appi.ajp.162.5.947

Seeman, P., & Lee, T. (1975). Antipsychotic drugs: direct correlation between clinical potency and presynaptic action on dopamine neurons. Science, 188(4194), 1217–1219. https://doi.org/10.1126/science.1145194

Seeman, M. V. (1986). Current outcome in schizophrenia: women vs men. Acta Psychiatrica Scandinavica, 73(6), 609–617. https://doi.org/10.1111/j.1600-0447.1986.tb02732.x

Seidman, L. J., Giuliano, A. J., Meyer, E. C., Addington, J., Cadenhead, K. S., Cannon, T. D., … Cornblatt, B. A. (2010). Neuropsychology of the prodrome to psychosis in the NAPLS Consortium: Relationship to family history and conversion to psychosis. Archives of General Psychiatry, 67(6), 578–588. https://doi.org/10.1001/archgenpsychiatry.2010.66

Selten, J. P., & Cantor-Graae, E. (2007). Hypothesis: Social defeat is a risk factor for schizophrenia? British Journal of Psychiatry, 191(SUPPL. 51). https://doi.org/10.1192/bjp.191.51.s9

Selten, J. P., Veen, N. D., Hoek, H. W., Laan, W., Schols, D., van der Tweel, I., … Kahn, R. S. (2007). Early course of schizophrenia in a representative Dutch incidence cohort. Schizophrenia Research, 97(1–3), 79–87. https://doi.org/10.1016/j.schres.2007.07.008

Shepherd, M., Watt, D., Falloon, I., & Smeeton, N. (1989). The natural history of schizophrenia: a five-year follow-up study of outcome and prediction in a representative sample of schizophrenics. Psychological Medicine. Monograph Supplement, 15, 1–46. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2798648

Simpson, G. M., Lee, J. H., Zoubok, B., & Gardos, G. (1979). A rating scale for tardive dyskinesia. Psychopharmacology, 64(2), 171–179. https://doi.org/10.1007/BF00496058

Sokoloff, P., Giros, B., Martres, M. P., Bouthenet, M. L., & Schwartz, J. C. (1990). Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. Nature, 347(6289), 146–151. https://doi.org/10.1038/347146a0

Stentebjerg-Olesen, M., Jeppesen, P., Pagsberg, A. K., Fink-Jensen, A., Kapoor, S., Chekuri, R., … Correll, C. U. (2013). Early Nonresponse Determined by the Clinical Global Impressions Scale Predicts Poorer Outcomes in Youth with Schizophrenia Spectrum Disorders Naturalistically Treated with Second-Generation Antipsychotics. Journal of Child and Adolescent Psychopharmacology, 23(10), 665–675. https://doi.org/10.1089/cap.2013.0007

Stępnicki, P., Kondej, M., & Kaczor, A. A. (2018). Current Concepts and Treatments of Schizophrenia. Molecules, 23(8), 2087. https://doi.org/10.3390/molecules23082087

Strauss, J. S., & Carpenter, W. T. (1977). Prediction of outcome in schizophrenia: III. Five-year outcome and its predictors. Archives of General Psychiatry. https://doi.org/10.1001/archpsyc.1977.01770140049005

Strous, R. D., Alvir, J. M. J., Robinson, D., Gal, G., Sheitman, B., Chakos, M., & Lieberman, J. A. (2004). Premorbid functioning in schizophrenia: Relation to baseline symptoms, treatment response, and medication side effects. Schizophrenia Bulletin. https://doi.org/10.1093/oxfordjournals.schbul.a007077

Tandon, R., Nasrallah, H. A., & Keshavan, M. S. (2009). Schizophrenia, "just the facts" 4. Clinical features and conceptualization. Schizophrenia Research, 110(1–3), 1–23. https://doi.org/10.1016/j.schres.2009.03.005

Tarsy, D., & Baldessarini, R. (1986). Movement Disorders Induced by Psychotherapic Agents. In N. Shah & A. Donald (Eds.), Movement Disorders (pp. 365–301). New York and London: Plenum Publishing Corp.

Tarsy, D., & Baldessarini, R. J. (2006). Epidemiology of tardive dyskinesia: Is risk declining with modern antipsychotics? Movement Disorders, 21(5), 589–598. https://doi.org/10.1002/mds.20823

Thakker, J., & Ward, T. (1998). Culture and classification: The cross-cultural application of the DSM- IV. Clinical Psychology Review, 18(5), 501–529. https://doi.org/10.1016/S0272-7358(97)00107-4

Thompson, A., Nelson, B., & Yung, A. (2011). Predictive validity of clinical variables in the "at risk" for psychosis population: International comparison with results from

the North American Prodrome Longitudinal Study. Schizophrenia Research, 126(1–3), 51–57. https://doi.org/10.1016/j.schres.2010.09.024

Thorup, A., Albert, N., Bertelsen, M., Petersen, L., Jeppesen, P., Le Quack, P., … Nordentoft, M. (2014). Gender differences in first-episode psychosis at 5-year follow-up-two different courses of disease? Results from the OPUS study at 5-year follow-up. European Psychiatry. https://doi.org/10.1016/j.eurpsy.2012.11.005

Tienari, P., Wynne, L.C., Sorri, A., et al. (2004). Genotype–environment interaction in schizophrenia spectrum disorder. Long-term follow-up study of Finnish adoptees. Br. J. Psychiatry, 184, 216–222. Retrieved from http://bjp.rcpsych.org/content/184/3/216.full

Tienari, P., Wynne, L. C., Läksy, K., Moring, J., Nieminen, P., Sorri, A., … Wahlberg, K.-E. (2003). Genetic Boundaries of the Schizophrenia Spectrum: Evidence From the Finnish Adoptive Family Study of Schizophrenia. American Journal of Psychiatry, 160(9), 1587–1594. https://doi.org/10.1176/appi.ajp.160.9.1587

Tsuang, M. T. (1978). Suicide in Schizophrenics, Manics, Depressives, and Surgical Controls: A Comparison with General Population Suicide Mortality. Archives of General Psychiatry, 35(2), 153–155. https://doi.org/10.1001/archpsyc.1978.01770260031002

Van Putten, T., May, P. R. A., & Marder, S. R. (1984). Response to antipsychotic medication: The doctor's and the consumer's view. American Journal of Psychiatry, 141(1), 16–19. https://doi.org/10.1176/ajp.141.1.16

Van Tol, H. H. M., Bunzow, J. R., Guan, H.-C., Sunahara, R. K., Seeman, P., Niznik, H. B., & Civelli, O. (1991). Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. Nature, 350(6319), 610–614. https://doi.org/10.1038/350610a0

Ventura, J., Subotnik, K. L., Guzik, L. H., Hellemann, G. S., Gitlin, M. J., Wood, R. C., & Nuechterlein, K. H. (2011). Remission and recovery during the first outpatient year of the early course of schizophrenia. Schizophrenia Research, 132(1), 18–23. https://doi.org/10.1016/j.schres.2011.06.025

Volkow, N. D., & Morales, M. (2015). The Brain on Drugs: From Reward to Addiction. Cell, 162(4), 712–725. https://doi.org/10.1016/j.cell.2015.07.046

Voruganti, L. N., & Awad, A. G. (2006). Subjective and behavioural consequences of striatal dopamine depletion in schizophrenia--findings from an in vivo SPECT study. Schizophr Res, 88(1–3), 179–186. https://doi.org/10.1016/j.schres.2006.07.012

Walder, D. J., Faraone, S. V., Glatt, S. J., Tsuang, M. T., & Seidman, L. J. (2014). Genetic liability, prenatal health, stress and family environment: Risk factors in the Harvard Adolescent Family High Risk for Schizophrenia Study. Schizophrenia Research, 157(1–3), 142–148. https://doi.org/10.1016/j.schres.2014.04.015

Walther, S., & Mittal, V. A. (2017). Motor System Pathology in Psychosis. Current Psychiatry Reports, 19(12). https://doi.org/10.1007/s11920-017-0856-9

Ward, K. M., & Citrome, L. (2018). Antipsychotic-Related Movement Disorders: Drug-Induced Parkinsonism vs. Tardive Dyskinesia—Key Differences in Pathophysiology and Clinical Management. Neurology and Therapy. https://doi.org/10.1007/s40120-018-0105-0

Weickert, C. S., Weickert, T. W., Pillai, A., & Buckley, P. F. (2013). Biomarkers in Schizophrenia: A Brief Conceptual Consideration. Disease Markers, 35(1), 3–9. https://doi.org/10.1155/2013/510402

Weiden, P. J., Mann, J. J., Haas, G., Mattson, M., & Frances, A. (1987). Clinical nonrecognition of neuroleptic-induced movement disorders: A cautionary study. American Journal of Psychiatry, 144(9), 1148–1153. https://doi.org/10.1176/ajp.144.9.1148

Weinberger, D. R. (1987). Implications of Normal Brain Development for the Pathogenesis of Schizophrenia. Archives of General Psychiatry, 44(7), 660–669. https://doi.org/10.1001/archpsyc.1987.01800190080012

WHO. (1993). ICD-10 Classification of Mental and Behavioral Disorders. Diagnostic Criteria for Research. World Health Organization, Geneva. Geneve: World Health Organisation.

Wiersma, D., Nienhuis, F. J., Slooff, C. J., & Giel, R. (1998). Natural course of schizophrenic disorders: A 15-year followup of a Dutch incidence cohort. Schizophrenia Bulletin, 24(1), 75–85. https://doi.org/10.1093/oxfordjournals.schbul.a033315

Wildenauer, D. B., Schwab, S. G., Albus, M., Hallmayer, J., Lerer, B., Maier, W., … Matise, T. C. (1996). Additional Support for Schizophrenia Linkage on Chromosomes 6 and 8: A Multicenter Study. American Journal of Medical Genetics, 67(6), 580–594. https://doi.org/10.1002/(SICI)1096-8628(19961122)67:6<580::AID-AJMG11>3.0.CO;2-P

Winton-Brown, T. T., Fusar-Poli, P., Ungless, M. A., & Howes, O. D. (2014). Dopaminergic basis of salience dysregulation in psychosis. Trends in Neurosciences, 37(2), 85–94. https://doi.org/10.1016/j.tins.2013.11.003

Woods, S. W., Morgenstern, H., Saksa, J. R., Walsh, B. C., Sullivan, M. C., Money, R., … Glazer, W. M. (2010). Incidence of tardive dyskinesia with atypical versus conventional antipsychotic medications: A prospective cohort study. Journal of Clinical Psychiatry, 71(4), 463–474. https://doi.org/10.4088/JCP.07m03890yel

Wyatt, R. J., Alexander, R. C., Egan, M. F., & Kirch, D. G. (1988). Schizophrenia, just the facts. What do we know, how well do we know it? Schizophrenia Research. https://doi.org/10.1016/0920-9964(88)90034-5

Yoshida, K., Bies, R. R., Suzuki, T., Remington, G., Pollock, B. G., Mizuno, Y., … Uchida, H. (2014). Tardive dyskinesia in relation to estimated dopamine D2 receptor occupancy in patients with schizophrenia: Analysis of the CATIE data. Schizophrenia Research, 153(1–3), 184–188. https://doi.org/10.1016/j.schres.2014.01.017

Zhang, J.-P., Gallego, J. A., Robinson, D. G., Malhotra, A. K., Kane, J. M., & Correll, C. U. (2013). Efficacy and Safety of Individual Second-Generation vs First-Generation Antipsychotics in First Episode Psychosis: A Systematic Review and Meta-analysis. International Journal of Neuropsychopharmacology, 16(6), 1205–1218. https://doi.org/10.1017/S1461145712001277.Efficacy

Zhuo, C., Tao, R., Jiang, R., Lin, X., & Shao, M. (2017). Cancer mortality in patients with schizophrenia: Systematic review and meta-analysis. British Journal of Psychiatry, 211(1), 7–13. https://doi.org/10.1192/bjp.bp.116.195776

Zubin, J., & Spring, B. (1977). Vulnerability: A new view of schizophrenia. Journal of Abnormal Psychology, 86(2), 103–126. https://doi.org/10.1037/0021-843X.86.2.103

10 ANNEXES