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THE CHAT STUDY:
CLOZAPINE HALOPERIDOL ARIPIPRAZOLE TRIAL

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INDEX

1 ABSTRACT

BACKGROUND

Schizophrenia is a disabling mental disorder. It affects as much as 1% of the population worldwide. A proportion of one fifth to one third of patients with schizophrenia derive little or no benefit from treatment with first or second generation antipsychotics. In these treatment refractory patients, clozapine has been shown to be the treatment of choice. Unfortunately, however, approximately one third of treatment-refractory patients have persistent positive symptoms. The need to provide real-world suggestions for patients who do not have an optimal response to clozapine has prompted European and American treatment guidelines to recommend the concurrent prescription of a second antipsychotic in addition to clozapine in partially responsive patients, with no indication on which agent should be prescribed.

OBJECTIVE

The main clinical question to be answered by CHAT is the relative efficacy and tolerability of combination treatment with clozapine plus aripiprazole compared to combination treatment with clozapine plus haloperidol in patients with an incomplete response to treatment with clozapine over an appropriate period of time.

METHODS

The Clozapine Haloperidol Aripiprazole Trial (CHAT) is a prospective, multicentre, pragmatic, randomized, parallel group, superiority trial. Patients were assessed at baseline and after three, six and 12 months of follow-up. During the study, patients and clinicians were not blind to pharmacological treatments provided during the trial. However, outcome assessments based on rating scales

were performed by trained assessors masked to the allocated treatment. CHAT was undertaken in compliance with Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol was approved by Italian Medicine Agency (Agenzia Italiana del Farmaco) and received ethical approval in each participating site. All phases of CHAT were recorded following the Consolidated Standard of Reporting of Trials (CONSORT) statement.

RESULTS

106 patients were enrolled in the study and randomly assigned to treatment. After three months (13.2 vs 15.1%, p = 0.780), as well as after twelve months (30.8 vs 38.0%, p = 0.442), the analysis of the primary outcome revealed no difference in the proportion of patients who discontinued treatment between the aripiprazole and haloperidol groups.

CONCLUSIONS

This study indicates that augmentation of clozapine with aripiprazole offers no benefit with regard to treatment withdrawal and overall symptoms in schizophrenia as compared with augmentation with haloperidol. The analysis of the 12-month data from CHAT, confirm a trend of favourable advantage in the perception of adverse effects with aripiprazole, found out at 3-month analysis.

2 BACKGROUND

Schizophrenia is a mental disorder characterized by a disintegration of the process of thinking and of emotional responsiveness. It most commonly manifests as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking, and it is accompanied by significant social or occupational dysfunction. As a result of the many possible combinations of symptoms, there is debate about whether the diagnosis represents a single disorder or a number of discrete syndromes. Despite the etymology of the term from the Greek roots *skhizein* (*σχίζειν*, "to split") and *phrēn, phren-* (*φρήν, φρεν-*; "mind"), schizophrenia does not imply a "split mind" and it is not the same as dissociative identity disorder, also known as "multiple personality disorder" or "split personality", a condition with which it is often confused in public perception (Picchioni and Murray, 2007). The original name for this illness, “dementia praecox,” was coined by Emil Kraepelin, a German psychiatrist in the late nineteenth and early twentieth century, whose description of the illness remains a guiding force for modern investigators.

Schizophrenia is a relatively common illness and it is certainly the most common form of psychotic disorder. The mean incidence of schizophrenia reported in epidemiological studies, when the diagnosis is limited to core criteria and corrected for age, is 0.11 per 1000 (range 0.07–0.17 per 1000); if broader criteria are used, this figure doubles to 0.24 per 1000 (range 0.07–0.52 per 1000) (Broome *et al.* 2005; Jablensky *et al.* 1992).

Average rates for men and women are similar, although the mean age of onset is about 5 years greater in women (hence a lower female rate in adolescence), with a second smaller peak after the menopause. Although most patients fall ill in late

teenage or early adult years, the range of age of onset is wide: childhood onset may occur, and in some instances symptoms may not appear until the sixties.

The lifetime prevalence of schizophrenia is between 0.4 and 1.4% (Cannon and Jones, 1996). The National Survey of Psychiatric Morbidity in the UK found a population prevalence of probable psychotic disorder of 5 per 1000 in the age group 16 to 74 years (Singleton, 2000).

There may or may not be a prodrome before the actual onset of symptoms. In some cases the "pre-morbid personality" appears completely normal. In others, however, peculiarities may have been apparent for years or even decades before the onset. In cases where the prodrome began in childhood, the history may reveal introversion and peculiar interests. In cases where the prodrome began later, after the patient's personality was formed, family members may recall a stretch of time wherein the patient "changed" and was no longer "the same." Prior interests and habits may have been abandoned and replaced by a certain irritable seclusiveness, or perhaps suspiciousness.

The onset of symptoms per se may be acute or insidious. Acute onsets tend to span a matter of weeks or months and may be characterized by confusion or at times by depressive symptoms. Patients may recognize that something is wrong, and they may make some desperate attempts to bring some order into the fragmenting experience of life. By contrast, in cases with an insidious onset the patient may not be particularly troubled at all. Over many months or a year or more, evanescent changes may occur: fleeting whispers, vague intimations, or strange occurrences.

The possible causes of schizophrenia are not well understood. Genetics, early environment, neurobiology, psychological and social processes appear to be

important contributory factors; some recreational and prescription drugs appear to cause or worsen symptoms.

Current psychiatric research is focused on the role of neurobiology, but this inquiry has not isolated a single organic cause.

The evidence does not point to any single cause. Increasingly, it is thought that schizophrenia and related psychoses result instead from a complex interaction of multiple factors (Broome *et al.* 2005; Garety *et al.* 2007).

Much of the research evidence on the aetiology of schizophrenia is consistent with the long-standing 'vulnerability stress' model (Nuechterlein and Dawson, 1984). This paradigm suggests that individuals possess different levels of vulnerability to schizophrenia, which are determined by a combination of biological, social and psychological factors. It is proposed that vulnerability results in the development of problems only when environmental stressors are present. If there is great vulnerability, relatively low levels of stress might be sufficient to cause problems. If there is less vulnerability, problems develop only with higher levels of stress.

The model is consistent with a wide variety of putative causes of the disorder, as well as the differential relapse and readmission rates observed among people with schizophrenia. Recent research has therefore attempted to specify more precisely the nature of any vulnerability and of types of environmental stress. This includes biological hypotheses about brain biochemistry and pathology (Broome *et al.* 2005), and attempts to identify genes that confer susceptibility (Craddock *et al.* 2005). Biochemical theories have centred mainly on the 'dopamine hypothesis', for which there is enduring support (Kapur, 2003). This argues that schizophrenia might be related to problems in the regulation of the neurotransmitter dopamine in the prefrontal cortex.

Psychological factors can be divided into problems with basic cognitive functions, such as learning, attention, memory or planning, and biases in emotional and reasoning processes. problems in cognitive function are related to research in brain structure and function, while emotional processes may be linked to social factors. Studies of psychological factors thus provide a bridge between biological and social theories. Both types of psychological factor have been implicated in the development of symptoms of schizophrenia (Garety *et al.* 2001; Garety *et al.* 2007; Gray, 2011; Green, 1992; Hemsley, 1993).

Recently, depression and anxiety, which were previously considered unimportant by researchers, have been found to contribute to the symptoms of schizophrenia (Birchwood, 2003; Freeman and Garety, 2003; Krabbendam and van, 2005).

Estimates of the heritability of schizophrenia tend to vary owing to the difficulty of separating the effects of genetics and the environment although twin and adoption studies have suggested a high level of heritability. It has been suggested that schizophrenia is a condition of complex inheritance, with many different potential genes each of small effect, with different pathways for different individuals. At the same time, different social causes have been under light.

Recently there has been a resurgence of interest in investigating social and environmental factors. Living in an urban environment has been consistently found to be a risk factor for schizophrenia (Crow, 2008; O'Donovan *et al.* 2009). Social disadvantage has been found to be a risk factor, including poverty (Crow, 2008) and migration related to social adversity, racial discrimination, family dysfunction, unemployment or poor housing conditions (Selten *et al.* 2007). Childhood experiences of abuse or trauma have also been implicated as risk factors for a diagnosis of schizophrenia later in life (Janssen *et al.* 2004; MacMillan *et al.* 2001).

Parenting is not held responsible for schizophrenia but unsupportive dysfunctional relationships may contribute to an increased risk (Crow, 2008; Selten and Cantor-Graae, 2005).

There is now consistent evidence that migrant populations experience raised rates and especially

High rates have been found among certain minority ethnic groups (Cantor-Graae and Selten, 2005; Kirkbride *et al.* 2006). It is thought that this is most likely related to the high rates of social adversity and family disruption experienced by some migrant populations (Fearon *et al.* 2006; Selten and Cantor-Graae, 2005).

In a recent study of people with schizophrenia and a substance abuse disorder, over a ten year period, "substantial proportions were above cut-offs selected by dual diagnosis clients as indicators of recovery." (Gregg *et al.* 2007).

Although about half of all patients with schizophrenia use drugs or alcohol, and the vast majority use tobacco, a clear causal connection between drug use and schizophrenia has been difficult to prove. The two most often used explanations for this are "substance use causes schizophrenia" and "substance use is a consequence of schizophrenia", and they both may be correct (McLaren *et al.* 2010).

Schizophrenia is often described in terms of *positive* and *negative* (or deficit) symptoms (Sims A., 2002).

The term positive symptoms refers to symptoms that most individuals do not normally experience but are present in schizophrenia.

They include:

- *Hallucinations*: patients may hear things, often voices, or they may see things; hallucination of taste, touch, and smell may also occur. However, of all these, the hearing of voices is most characteristic of schizophrenia.

The voices may come from anywhere. They come from the air, from the television or radio, sometimes they are in clothing, often they are localized to certain parts of the body (they come from the bowels, the liver, from "just behind the ear."). They may be male or female; the patient may or may not be able to recognize the identity of the speaker. Most often, though, the voices are not recognized as belonging to anyone; they are from strangers. They may be clear and easily understood; sometimes they are deafening and compelling—"everything else is shut out." At other times they may be soft, "just a mumbling," indistinct and fading. What the voices say is extremely varied: however, certain themes are relatively common. Voices may comment on what the patient is doing. Often two voices argue with one another about the patient. Often the voice echoes or repeats what the patient thought. Thoughts are "audible"; they are "heard out loud"; they are repeated on the television.

At times "command hallucinations," or voices that tell the patient what to do, may be heard. At times these are imperious and irresistible; at other times they are soft, "suggestive" only. Sometimes they command innocuous things; the patient may be directed to shave again. At other times they may command the patient to commit suicide or to hurt others. Usually the commands can be resisted, but not always. Sometimes they are overwhelmingly compelling—"they must be obeyed." The patients generally hear only short phrases, perhaps single words. Only very rarely do the voices speak at length in a coherent way. Often the patient is tortured by the voices.

Rarely patients are encouraged or comforted by the voices. Most patients find the voices as real sounding as the voice of any other person. They may talk back to them out loud or may even argue with them.

Visual hallucinations, though common, play a relatively less prominent part in the clinical picture of schizophrenia than do auditory hallucinations. They may be poorly formed, indistinct, seen only "out of the corner of the eye." They may, however, be vivid and compellingly realistic. Strange people walk the halls; the devil in violent red appears in front of the patient; heads float through the air. Reptilian forms appear in the bath; things crawl in the food; a myriad of insects appear in the bedding.

Hallucinations of smell and taste, though not common, may be particularly compelling to the patient. Tastes, often foul and bitter, may appear on the tongue "from nowhere." Often, however, something is detected in food or drink. Patients may refuse all food and drink and declare that they have had enough poison already.

Hallucinations of touch, also known as haptic or tactile hallucinations, are relatively common. Something is crawling on them; a pricking is coming from behind. At night all manner of things are felt. Fluids are poured over the body; a caressing is felt, as are lips on all parts. Electrical sensations may be felt at any time. Sometimes patients may feel things inside their bodies.

- *Delusions:* they are almost universal in schizophrenia. The content of the delusions is extremely varied: patients may feel persecuted; they may have grandiose ideas; all manner of things may refer and pertain to them; thoughts may be broadcast, withdrawn, or inserted into them; they may feel influenced and controlled by outside forces; bizarre, loathsome events may occur. These beliefs may grow in the patient slowly. At first there may be only an inkling, a suspicion; only with time does conviction occur. Conversely, sudden enlightenment may occur; all may be immediately clear. Sometimes patients may have lingering doubts about the truth of these beliefs, but for most they are as self-evident as any

other belief. Occasionally patients may argue with those who disagree, but for the most part they do not press their case on the unbeliever. Most often the delusions are poorly coordinated with each other; typically they are contradictory and poorly elaborated. Occasionally, however, they may be systematized, and this is especially the case in the paranoid subtype.

Delusions of persecution are particularly common.

Grandiose delusions also occur frequently, often in conjugation with delusions of persecution.

Commonly most patients do not act on their delusions; rather they seem content to be comforted and sustained by them. Exceptions do occur, of course.

Delusions of reference are intimately tied to delusions of persecution or of grandeur. Here patients believe that otherwise chance occurrences or random encounters have special meaning for them. What was done refers to them; it pertains to them. There are no more coincidences in life, no accidental happenings. To the grandiose patient the events of creation are exalting; to the persecuted patient, walking the streets can provoke a terrifying self-consciousness. Everything is pregnant with meaning. Some patients may develop some peculiarly bizarre beliefs about thinking itself, known as thought broadcasting, thought withdrawal, and thought insertion. In thought broadcasting patients experience thoughts as being broadcast from their heads, as if by electricity. In thought withdrawal the patients' thoughts are removed, taken from them. The mind is left blank. Patients who experience this symptom of thought withdrawal may concurrently, if they happen to be speaking their thoughts, display the sign known as "thought blocking." Here, patients in the middle of speaking abruptly cease talking, and this happens precisely because they abruptly find themselves with no thoughts to express. In thought insertion, a phenomenon opposite to that of

thought withdrawal occurs. Here patients experienced the insertion of thoughts into their minds. The thoughts are alien, not their own; they were placed there by some other agency.

Another delusion is the delusion of doubles, also known as the "Capgras phenomenon," or the delusion of impostors. Here the patient believes that someone, or something, has occupied the body of another. Although the body looks the same and the voice is the same, indeed, for all intents and purposes, it is the same person, yet the patient knows without doubt that it is an impostor.

- *Disorganized speech:* this "formal thought disorder" is most often characterized as "loosening of associations"; less frequently it is referred to as incoherence or "derailment." The patient's speech becomes illogical; ideas are juxtaposed that have no conceivable connection. At its extreme, loosening of associations may present as a veritable "word salad." Here any inner connection among the various ideas and concepts is lost; it is as if they come at random. The thoughts are no longer "goal-directed"; they no longer cohere in pursuit of a common purpose. Patients seem little concerned about their incoherence.

Allied to loosening of associations are neologisms. These are words that occur in the normal course of the patient's speech and that the patient treats as an integral part of it, but that convey no more meaning to the listener than if they were from a long-dead foreign language. To the patient, however, they have as much meaning and status as any other word, but that meaning is private and inaccessible to the listener.

Negative symptoms are things that are not present in schizophrenic persons but are normally found in healthy persons, that is, symptoms that reflect the loss or absence of normal traits or abilities.

Common negative symptoms include:

- *Flatted or blunted affect and emotion*: lifeless and wooden facial expression accompanied by an absence or diminution of all feelings.

This is quite different from a depressed appearance. In depression patients appear drained or weighted down; there is a definite sense of something there. In flattening, however, patients seem to have nothing to express; they are simply devoid of emotion. They appear unmoved, wooden, and almost at times as if they were machines.

- *Alogia* : poverty of speech.

It is said to occur when patients, though perhaps talking a normal amount, seem to "say" very little. There is a dearth of meaningful content to what they say and speech is often composed of stock phrases and repetitions.

- *Poverty of thought:* far-reaching impoverishment of the entire thinking of the patient.

The patient may complain of having "no thoughts," that "the head is empty," that there are no "stirrings." Of its own accord nothing "comes to mind." If pressed by a question the patient may offer a sparse reply, then fail to say anything else.

- *Avolition:* lack of motivation.

It is referred to by Kraepelin as "annihilation of the will," is said to be present when patients have lost the capacity to embark on almost any goal-directed activity.

- *Anhedonia*: inability to experience pleasure.
- *Asociality:* lack of desire to form relationships.

Research suggests that negative symptoms contribute more to poor quality of life, functional disability, and the burden on others than do positive symptoms (Velligan DI and Alphs LD., 2008).

In one uncommon subtype, the person manifest signs of *catatonia*. Catatonic symptoms include negativism, catalepsy, posturing, stereotypies and echolalia or echopraxia:

- *Negativism:* mulish, automatic, almost instinctual opposition to any course of action suggested, demanded, or merely expected.
- *Catalepsy*: waxy flexibility.

It is characterized by a state of continual and most unusual muscular tension.

- *Posturing:* the patient, for no discernible reason, assumes and maintains a bizarre posture. One may keep the arms cocked; another stood bent at the waist to the side.
- *Stereotypies*: bizarre, perseverated behaviours.

A patient, for example, may march back and forth along the same line for hours; another may repeatedly dress and undress. Most patients can offer no reason for their senseless activity.

- *Echolalia* and *echopraxia*: patient's behaviour mirrors that of the other person, and, importantly, when this happens automatically, and in the absence of any request.

Diagnosis of schizophrenia is based on the self-reported experiences of the person, and abnormalities in behaviour reported by family members, friends or co-workers, followed by a clinical assessment by a psychiatrist, social worker, clinical psychologist, mental health nurse or other mental health professional.

The most widely used standardized criteria for diagnosing schizophrenia come from the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, version DSM-IV-TR, and the World Health Organization's International Statistical Classification of Diseases and Related Health Problems, the ICD-10. The latter criteria are typically used in European countries, while the DSM criteria are used in the United States and the rest of the world, as well as prevailing in research studies. The ICD-10 criteria put more emphasis on Schneiderian first-rank symptoms, although, in practice, agreement between the two systems is high (Kneisl C.and Trigoboff E, 2009).

According to the revised fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), to be diagnosed with schizophrenia, three diagnostic criteria must be met (American Psychiatric Association.Task Force on DSM-IV.(2000)., 2000):

1. **Characteristic symptoms**.

Two or more of the following, each present for much of the time during a one-month period (or less, if symptoms remitted with treatment).

- Delusions
- Hallucinations
- Disorganized speech, which is a manifestation of formal thought disorder
- Grossly disorganized behaviour (e.g. dressing inappropriately, crying frequently) or catatonic behaviour
- Negative symptoms: blunted affect (lack or decline in emotional response), alogia (lack or decline in speech), or avolition (lack or decline in motivation)

If the delusions are judged to be bizarre, or hallucinations consist of hearing one voice participating in a running commentary of the patient's actions or of hearing

two or more voices conversing with each other, only that symptom is required above.

The speech disorganization criterion is only met if it is severe enough to substantially impair communication.

2. **Social/occupational dysfunction**.

For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset.

3. **Duration**.

Continuous signs of the disturbance persist for at least six months. This six-month period must include at least one month of symptoms (or less, if symptoms remitted with treatment).

The DSM-IV-TR contains five sub-classifications of schizophrenia.

Subtypes of schizophrenia are characterized by particular constellations of symptoms and include the following: paranoid, catatonic, hebephrenic (or "disorganized"), simple (which has also been referred to as "simple deteriorative disorder"), and residual subtype.

Patients whose illness does not fall into any of these subtypes are said to have an "undifferentiated" subtype.

The different subtypes may have different prognoses. Furthermore, knowing the subtype allows one to predict with better confidence how any given patient might react in any specific situation.

Paranoid schizophrenia

It tends to have a later onset than the other subtypes and, it is characterized primarily by hallucinations and delusions. The delusions are generally persecutory and referential. In paranoid schizophrenia, more than in the other subtypes, the delusions may be somewhat systematized, even plausible. In most cases, however, inconsistencies appear, which, however, have no impact on the patients. Often, along with persecutory delusions, one may also see some grandiose delusions. Rarely, grandiose delusions may be more prominent than persecutory ones and may dominate the entire clinical picture.

Catatonic schizophrenia

It manifests in one of two forms: stuporous catatonia or excited catatonia.

In the stuporous form one sees varying combinations of immobility, negativism, mutism, posturing, and waxy flexibility.

In the excited form of catatonia one may see purposeless, senseless, frenzied activity, multiple stereotypies, and at times extreme impulsivity. Typically, despite their extreme activity, these patients remain for the most part withdrawn.

Rarely Stauder's lethal catatonia may occur. Here, as the excitation mounts over days or weeks, autonomic changes occur with hyperpyrexia, followed by coma and cardiovascular collapse. Although some patients with catatonic schizophrenia may display only one of these two forms, in most cases they are seen to alternate in the same patient. In some cases a form may last days, weeks, or longer, before passing through to the other. In other cases, however, a rapid and unpredictable oscillation from one form to another may occur.

Hebephrenic (disorganised) schizophrenia

It tends to have an earlier onset than the other subtypes and tends to develop very insidiously. Although delusions and hallucinations are present, they are relatively minor, and the clinical picture is dominated by bizarre behaviour, loosened associations, and bizarre and inappropriate affect.

Residual schizophrenia

In this subtype positive symptoms are present at a low intensity only.

Simple schizophrenia

Insidious and progressive development of prominent negative symptoms with no history of psychotic episodes. It has perhaps the earliest age of onset, often first beginning in childhood, and shows very gradual and insidious progression over many years. Delusions, hallucinations, and loosening of associations are sparse, and indeed are for the most part absent. Rather the clinical picture is dominated by the annihilation of the will, impoverishment of thought, and flattening of affect. Gradually over the years these patients fall away from their former goals and often become cold and distant with their former acquaintances. Occasionally some bizarre behaviour or a fragmentary delusion may be observed. For the most part, however, these patients do little to attract any attention.

Undifferentiated schizophrenia

It is said to be present when the clinical picture of any individual case does not fit well into one of the foregoing subtypes.

This is not uncommonly the case, and it also appears that in some instances the clinical picture, which initially did "fit" a subtype description, may gradually

change such that it no longer squares with one of the specific subtypes: this appears to be more common with the catatonic and hebephrenic subtypes than with paranoid or simple schizophrenia.

Before leaving this discussion of subtypes, it is appropriate to briefly discuss another proposal for subdividing schizophrenia, which is said by some to have more predictive and heuristic value than the classical sub typing just exposed.

Two subdivisions are proposed: "good prognosis," "reactive," or "type I" schizophrenia, and "poor prognosis," "process," or "type II" schizophrenia.

The contrasting characteristics of these two subdivisions are outlined in Table 1.

Table 1. type I and type II Schizophrenia.

	Type I	**Type II**
Premorbid personality	Normal	Poor adjustment
Age of onset	Late, often adult years	Early
Mode of onset	Acute	Gradual and insidious
Symptoms associated with onset	Confusion and depression	Few
Kind of symptoms	Positive	Negative
Ventriculomegaly on CT scan	Absent	Present
Course	More favourable	Unfavourable

Although this "good prognosis"/"poor prognosis" scheme is useful, many patients do not fit neatly into type I or type II but rather evidence a mixture of features of both types.

In most cases, schizophrenia exhibits one of two overall patterns.

In one, the course of symptoms is waxing and waning, whereas in the other there is a more or less stable chronicity.

The waxing and waning course is marked by exacerbations and partial remissions. The pattern of these changes is often quite irregular, as are the durations of the exacerbations and partial remissions, ranging from weeks, to months, or even years.

Some patients, during episodes of partial remission of the "positive" symptoms, may develop a sustained and pervasive depressed mood accompanied by typical vegetative symptoms. This condition, often referred to as a "post psychotic depression", increases the risk of suicide. Importantly, such a post psychotic depression should not be confused with the frequent, transient, and isolated depressive symptoms seen during an exacerbation of the other symptoms of the illness. At times, exacerbations may be precipitated by life stresses; however, at other times they simply happen. Among the stresses that can precipitate exacerbations, living in a family with high "expressed emotion" is important. Such family members tend to be intrusive, critical, and over-involved, and patients exposed to such an onslaught, even when provided with optimum medical treatment, are likely to relapse. Some patients experience this fluctuating course for their entire lives; in many others, however, after 5 to 20 years, this pattern gives way to one of stable chronicity. The stable chronicity seen in some patients may appear in some cases after the initial onslaught of symptoms seen at the onset of the disease has dampened, and in others, as for example those with simple schizophrenia, it may be apparent from the onset itself. Over long periods of time, patients with this course may show very slow progression until the disease eventually "burns out" leaving them in a deteriorated state.

The classical subtype diagnosis may allow for some prediction as to course. Those with paranoid or catatonic schizophrenia tend to pursue a fluctuating course, and of the two the eventual outcome appears to be worse for the catatonic subtype.

The hebephrenic and simple subtypes tend to pursue either a stable or progressively deteriorating chronicity, and of the two the simple subtype seems to often undergo the greatest deterioration.

Before leaving this discussion of the course of the disease, it is appropriate to consider whether or not schizophrenia, in the natural course of events, and in the absence of pharmacological treatment, ever undergoes a full and complete remission.

Certainly, far-reaching remissions have been documented; indeed, in many cases patients may appear at first glance to be recovered, and if one's definition of "recovery" or "remission" is broad enough, as is the case in many published studies, one might say that a remission did occur. However, on closer inspection one may generally find lingering residual symptoms in these "recovered" patients, such as fleeting hallucinations, odd thoughts, mannerisms or a certain poverty of thought. Thus, although "social" recoveries in the absence of treatment, although rare, do occur, it is very unlikely that, in the natural course of the disease, there is ever a *restitutio ad integrum.*

Most of times this disease lead to important complications.

Academic and business failure are common; most patients are incapable of sustaining intimate relationships. About half attempt suicide, and about 10% succeed. Most suicides occur early in the course of the illness; depressive symptoms, as are seen in post psychotic depression, male sex and unemployment increase the risk.

A not uncommon, but often overlooked, complication is hyponatremia. Some patients become "compulsive water drinkers"; however, the hyponatremia appears not to be caused solely by excessive intake of water. The renal tubule cells appear

to be hypersensitive to ADH, leading to a urine osmolality that is less than maximally dilute relative to the degree of hyponatremia.

There are no reliable markers for the later development of schizophrenia although research is being conducted into how well a combination of genetic risk plus non-disabling psychosis-like experience predicts later diagnosis (Phillips *et al.* 2002). People who fulfill the 'ultra high-risk mental state' criteria, that include a family history of schizophrenia plus the presence of transient or self-limiting psychotic experiences, have a 20–40% chance of being diagnosed with the condition after one year.

The use of psychological treatments and medication has been found effective in reducing the chances of people who fulfill the 'high-risk' criteria from developing full-blown schizophrenia. However, the treatment of people who may never develop schizophrenia is controversial, in light of the side-effects of antipsychotic medication; particularly with respect to the potentially disfiguring tardive dyskinesia and the rare but potentially lethal neuroleptic malignant syndrome.

The most widely used form of preventative health care for schizophrenia takes the form of public education campaigns that provide information on risk factors and early symptoms, with the aim to improve detection and provide treatment earlier for those experiencing delays.

The new clinical approach early intervention in psychosis is a secondary prevention strategy to prevent further episodes and prevent the long term disability associated with schizophrenia.

Until the 1950s, the treatment and management of schizophrenia generally took place in large asylums where people remained confined for much of their lives.

Although government policy initiated a programme of gradual closure of these large hospitals and the rehousing of the residents in the community, this process

was greatly assisted by the introduction of antipsychotic drugs, such as chlorpromazine, thioridazine and haloperidol. Antipsychotic medication would become the mainstay of treatment for the rest of the 20th century.

Patients may also be seen in supportive psychotherapy, either on an individual basis or in a group, and in social skills training groups.

A "token economy" approach may be required for severely debilitated patients.

Families may also be seen, not only for educational purposes, but also to enable them to lessen the kinds of family interactions that tend to be followed by relapse. Assistance may be required to enable the patient to secure housing and employment.

The effectiveness of schizophrenia treatment is often assessed using standardized methods, one of the most common being the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.* 1987). Management of symptoms and improving function is thought to be more achievable than a cure.

Nowadays, within both hospital and community settings, antipsychotic medicines remain the primary treatment for schizophrenia.

In general, the term "antipsychotics" refers to the class of drugs used to treat schizophrenia and other psychotic illness. The antipsychotic potency of most antipsychotics is directly proportional to their ability to block dopamine receptors in the brain, although the exact mechanism by which they exert their antipsychotic effect is probably more complicated than this. They vary greatly in their selectivity for dopamine receptors, many also having significant effects on acetylcholine, norepinephrine, histamine and serotonin pathways. Unfortunately, using this class of drugs, a wide range of side effects is to be expected.

Of these the most common are:

- ***Extrapyramidal side effects***: dystonic reactions (such as oculogyric, spasm and torcicollis), pseudoparkinsonism (tremor, bradykinesia and rigidity), akathisia (a subjectively unpleasant state of motor restlessness) and tardive dyskinesia.
- ***Hyperprolactinaemia***: it is an expected phenomenon since prolactin is under the inhibitory control of dopamine. Hyperprolactinaemia can lead to galactorrhoea, amenorrhoea, gynaecomastia, hypogonadism, sexual dysfunction and increased risk of osteoporosis (Dickson *et al.* 2000; Smith *et al.* 2002). Long-stay psychiatric female inpatients have been noted to have nine fold increase in the risk of breast cancer when compared to the normal population (Halbreich *et al.* 1996). Although other risk factors are undoubtedly important in this group of patients, prolonged hyperprolactinaemia is likely to be a contributing factor. A measurement of serum prolactin can be a useful indicator that the (older, first generation) antipsychotic drug is being taken and is reaching CNS dopamine receptors.
- ***Reduced seizure threshold***: grand mal seizures are a recognized side effect of antipsychotic therapy (the higher the dose, the greater the risk).
- ***Postural hypotension***: this side-effect is mediated through adrenergic alpha1-blockade, and so can usually be predicted for any drug with significant antagonist activity at this receptor.
- ***Anticholinergic side-effects***: dry mouth (which may contribute to dental decay, ill-fitting dentures) , blurred vision (which can contribute to fall in the elderly) and constipation (impaction can occur). Anticholinergic effects may also have a detrimental impact on cognitive functioning.

- ***Neuroleptic malignant syndrome*** (NMS): it is a potentially life-threatening complication of neuroleptic treatment, with the mortality rate estimated as being up to 20%. It may occur in as 0.5% of patients treated with first-generation antipsychotics and is thought to be greatly under-diagnosed. The main symptoms of NMS are mild hyperthermia, fluctuating consciousness, muscular rigidity, autonomic instability and severe EPSEs (primarily rigidity). Serum CPK is always raised. The enormous load of muscle breakdown products can lead to severe renal damage. The syndrome is believed to be caused by the rapid blockade of hypothalamic and striatal dopamine receptors, leading to a "resetting" of the thermoregulatory systems and severe skeletal muscle spasm, which contributes to a considerable heat load that cannot be dissipated.
- ***Weight gain***: people with schizophrenia, in comparison to the general population, are more likely to be overweight and have increased quantities of visceral fat (Meyer, 2001; Thakore *et al.* 2002). A substantial proportion of patients will gain 7% of their baseline body weight, which increases the risk of obesity-related morbidity (for example type 2 diabetes, heart diseases and some type of cancers).

Moreover some antipsychotic drugs are sedative, some are cardio-toxic and many are associated with idiosyncratic side-effects.

Furthermore antipsychotic treatment is a risk factor for venous thromboembolism (Zornberg and Jick, 2000), and in elderly patients who have dementia for stroke (Gill *et al.* 2005).

The antipsychotics may be broadly divided into two groups, namely "first generation," or "typical" drugs, and "second generation," or "atypical" drugs.

Commonly used first generation antipsychotics include haloperidol, fluphenazine and chlorproamzine.

There is an ever growing number of second generation drugs, which now includes clozapine, olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole. The main advantage of these second-generation ('atypical') antipsychotics (SGAs) appears to be that they have a lower liability for acute EPS and tardive dyskinesia. All the antipsychotics have a well-established evidence for efficacy in both the treatment of acute psychotic episodes and relapse prevention over time (Janicak, 1993).

However, despite this, considerable problems remain.

A significant proportion of service users have a poor response to conventional antipsychotic drugs and continue to show moderate to severe psychotic symptoms (both positive and negative).

Approximately one fifth to one third of patients with schizophrenia, in fact, derives little or no benefit from monotherapy with first-line antipsychotics (Conley and Kelly, 2001). In these treatment-refractory patients only one antipsychotic drug, clozapine, has a specific license for the treatment and it has been shown to be the treatment of choice (Kane *et al.* 1988a; Rosenheck *et al.* 1997).

Clozapine is the archetypal antipsychotic. It has been around since the 1960s and was withdrawn from use after an association with neutropenia (incidence 3%) and agranulocytosis (0.8%) was made. The pivotal study by Kane et al.(Kane *et al.* 1988b) in the late 1980s proved that clozapine was more effective than conventional antipsychotics, and it was reintroduced in the UK with compulsory haematological monitoring. Patients must have a full blood count performed weekly for the first 18 weeks (when the risk of

neutropenia/agranulocytosis is greatest), fortnightly until 52 weeks of treatment, and then monthly thereafter if haematologically stable (the incidence of agranulocytosis after one year is similar to that associated with the phenothiazines).

Clozapine treatment reduces suicidality and the data are sufficient for specific labelling for this indication in the USA.

The pharmacology of clozapine is unusual compared with other antipsychotics in that it only binds weakly to D1 and D2 receptors, while having an affinity for D4, 5HT2, 5HT3, alpha1 and alpha2 adrenergic, and Ach M1 and H1 receptors. Which one/combination of any of these effects is responsible for the superior clinical profile of clozapine is a subject of extensive speculation, but as of yet, no firm conclusion.

Clozapine also has a unique side-effect profile in that it has been associated with an extremely low incidence of EPSEs, and is thought not to cause/precipitate tardive dyskinesia. Moreover it does not raise prolactin levels and so is not associated with amenorrhoea.

Nevertheless, approximately one third of treatment-refractory patients have persistent positive and negative symptoms despite clozapine monotherapy of adequate dosage and duration (Kane *et al.* 1988a; Rosenheck *et al.* 1997). In these patients, partially responsive to clozapine, augmentation with haloperidol or other antipsychotic drugs is one of the most frequently therapeutic options employed in clinical practice, although the background evidence is limited and contradicttory (Mouaffak *et al.* 2006; Paton *et al.* 2007).

Haloperidol is a very potent D2 blocker. It is the most widely prescribed drug in the group of butyrophenones. Barbui and colleagues, who systematically reviewed the available literature, included six placebo-controlled randomized

trials conducted in Western countries and 15 randomized trials conducted in China. The analysis revealed that, in comparison with addition of placebo, a second antipsychotic in addition to clozapine had modest to absent benefit (Barbui *et al.* 2009a). Additionally, a recent Cochrane review, which assessed the efficacy and tolerability of various clozapine combination strategies with antipsychotics in people with treatment-resistant schizophrenia, included three small randomized controlled trials that failed to show if any particular combination strategy was superior to the others (Cipriani *et al.* 2009a).

In recent years the availability of newer antipsychotic agents has increased the therapeutic options available in the management of clozapine partial responders and, among these newer agents, anecdotal reports have hypothesised a promising role for aripiprazole (Bowles and Levin, 2003; Marder *et al.* 2003).

Aripiprazole is a partial agonist at D2 receptors: full binding to D2 receptors reduces dopaminergic neuronal activity by about 30% (in the absence of dopamine, aripiprazole acts as a weak agonist). It is a potent antagonist at 5HT2a receptors and a partial agonist at 5HT1a receptors.

In contrast to some of the other atypical antipsychotic agents, treatment with aripiprazole appears to be associated with minimal weight gain and minimal negative impact on metabolic parameters, a key aspect given that these adverse effects might occur during clozapine treatment (Cipriani *et al.* 2009d; Zou, 2004). In terms of positive symptoms, it has been suggested that the combination of clozapine and aripiprazole may lead to greater D2 receptor antagonism in mesolimbic pathways, and, additionally, may combine D2 and D4 antagonism (although the role of D4 receptors in antipsychotic efficacy is unclear). A challenging neurobiological rationale, with a highly synergistic antipsychotic potency without increasing the risk of adverse effects, has therefore been

proposed (Tapp *et al.* 2003). Henderson and colleagues, who conducted a six-week open label trial to examine the effects of adjunctive aripiprazole in clozapine-treated subjects, showed that this combination had little or no effect in terms of psychotic symptoms, but was associated with a significant decrease in weight, body mass index, fasting total serum cholesterol and total triglycerides (Rendell *et al.* 2004). The only randomised placebo-controlled trial published so far, which included 62 clozapine-treated patients with refractory schizophrenia that were randomly assigned to double-blind combination treatment with aripiprazole or placebo, showed that aripiprazole did not lead to better control of symptom severity after 8 weeks of treatment, but benefits were observed in terms of negative symptoms (Kahn *et al.* 2008a).

The only randomized, placebo-controlled trial conducted so far showed that, in comparison with augmentation with placebo, augmentation with aripiprazole was not associated with increased efficacy, but was associated with less adverse effects (Chang *et al.* 2008).

Despite this paucity of positive results, the need to provide real-world suggestions for patients who do not have an optimal response to clozapine has prompted European and American treatment guidelines to recommend the concurrent prescription of a second antipsychotic in addition to clozapine in partially responsive patients, with no indication on which agent should be prescribed.

In the randomized study presented in this thesis we therefore compared the relative effectiveness and tolerability of two clozapine combination strategies, namely clozapine and aripiprazole versus clozapine and haloperidol, a reference therapeutic option often employed under ordinary circumstances (Schumacher *et al.* 2003; Sernyak and Rosenheck, 2004).

3 METHODS

Italian legislation on independent trials

The Italian context of care is an ideal setting for independent randomised trials, given the implementation of a National Law (Decreto Ministeriale 17/12/04) that formally recognised the public health value of independent studies investigating the real-world effectiveness of already marketed pharmacological treatments. In 2004 a Ministerial Decree was issued establishing rules to help implement pragmatic independent phase IV clinical trials. In essence, the Decree states that if the following set of conditions are met:

- the study coordinating centre is independent of drug company support;
- study results can be disseminated autonomously;
- there is no personal financial interest in studying the drugs included in the trial;
- the study drugs are licensed for the indication to be investigated;
- then the National Health Service (NHS) materially supports the conduct of the trial in three ways:
- drug costs are paid by the NHS;
- there are no fees for submitting the study protocol to the local Ethics Committees;
- continuing medical education credits are provided to local investigators.

Considering that all above mentioned criteria are met by the Clozapine Haloperidol Aripiprazole Trial (CHAT), we took fully advantage of such legislation. In particular, drug costs (clozapine, aripiprazole and haloperidol) are

covered by the local health authorities, with two advantages: first, we had the possibility to carry out this study on a low budget, independently from drug companies and from other agencies; second, the drugs under study are prescribed in a way that is identical to that normally followed under real-word circumstances, with obvious advantages in terms of generalizability of study findings.

Pragmatic versus explanatory design

In recent years there has been a renewal of interest in pragmatic trials (also called practical, effectiveness or management trials), that is for studies that randomly assign real-world patients to licensed drugs with the aim of assessing their effectiveness (Schwartz and Lellouch, 1967a; Zwarenstein *et al.* 2008). While explanatory (or phase III) trials answer questions about whether an intervention can work under ideal conditions (efficacy), pragmatic (or phase IV) trials attempt to answer questions about whether an intervention will work in the real world. Explanatory trials are usually carried out by the pharmaceutical industry, while pragmatic trials are more often undertaken by groups of clinical researchers. Recent examples of pragmatic trials include the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (Lieberman *et al.* 2005) and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) (Jones *et al.* 2006).

In Italy a seminal pragmatic study was an unblinded trial of intravenous streptokinase in early acute myocardial infarction that enrolled 11,806 patients in one hundred and seventy-six coronary care units (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI), 1986). The first report of this influential study was published in 1986 and in subsequent years there was an ongoing debate about the need to support such research.

In the field of mental health, however, only in very recent years criticism has focused on the current standard of the design of explanatory clinical trials. These studies typically enrol highly selected patients that are shortly followed and assessed with rating scales that are seldom used in clinical practice. In Italy this criticism has progressively led mental health professionals to constitute research networks with the aim of developing pragmatic studies. Such studies, ideally, are intended to answer real-world questions by enrolling everyday patients to be followed in the long-term using pragmatic outcome criteria commonly used in practice. Pragmatic measures include suicide attempts, treatment switching, hospitalization, school failure or truancy, job loss, or treatment discontinuation (Barbui and Cipriani, 2007; March *et al.* 2005; Schwartz and Lellouch, 1967b). CHAT is the first Italian example of this new attitude (Barbui C., 2007),and other studies will soon follow (Barbato A. *et al.* 2008).

Design of the clozapine haloperidol aripiprazole trial (CHAT)

The principal clinical question to be answered by CHAT was the relative effectiveness and tolerability of combination treatment with clozapine plus aripiprazole compared to combination treatment with clozapine plus haloperidol in patients with an incomplete response to treatment with clozapine over an appropriate period of time.

CHAT is a prospective, multicentre, randomized, parallel-group, superiority trial that follows patients over a period of 12 months. Consecutive patients meeting the trial entry criteria were randomly assigned to combination with aripiprazole or haloperidol. Patients and clinicians were not blind to pharmacological treatments provided during the trial. Patients were assessed at baseline, at 3, 6 and 12 months.

According to Italian legislation, ethics approval was received in each participating site.

All phases of CHAT were recorded following the CONSORT statement (Moher *et al.* 2001).

Pharmacological treatments

In order to resemble everyday clinical practice, clinicians were allowed to prescribe the allocated pharmacological treatments (starting dose and dose changes) according to clinical status and circumstances.

All dose changes were recorded. Following randomization, treatment was to be taken daily for 1 year unless some clear reason to stop develops. Before random allocation, patients were asked to discontinue any antipsychotic drugs other than clozapine. Long-acting antipsychotic drugs needed to be discontinued for at least two weeks before random allocation. All other concomitant medications were permitted.

Routine care outside the trial continues as usual. During the study, participants were seen as often as clinically indicated with no extra visits required for the trial.

Power analysis for sample size calculation

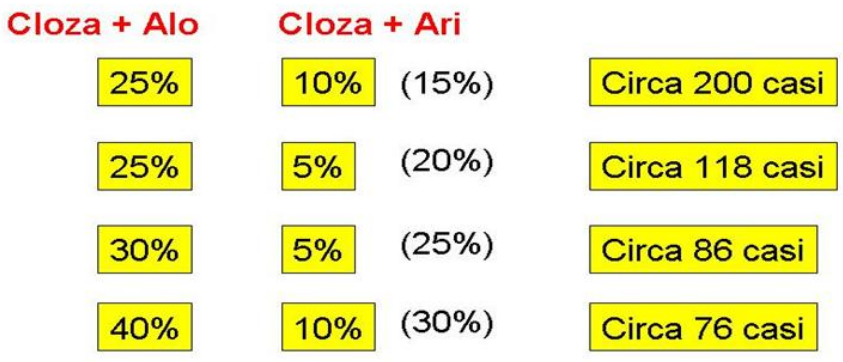
At the time of development of the CHAT, only one antipsychotic trial employed discontinuation by any cause as the primary endpoint (Lieberman *et al.* 2005). On the basis of this trial, it was initially hypothesised a withdrawal proportion from allocated treatment within 3 months (primary study endpoint) of 25% in the group treated with clozapine plus haloperidol (control group). Moreover, it was hypothesised that the augmentation with aripiprazole (experimental group) would show a clinically significant advantage by producing a withdrawal proportion of

10%. A sample size of 194 patients (97 in each group) achieves 80% power to detect a difference of 15% between the two withdrawal proportions. The test statistic used is the two-sided Z test with pooled variance. The significance level of the test is targeted at 5%. Assuming that 10% of the participants could be lost within 3 months, or could not provide valid data at month 3, 216 (=194/0.90) patients should have been enrolled in order to obtain 194 evaluable subjects (Chow *et al.* 2003; Cipriani *et al.* 2009c). Therefore, the target total sample size for CHAT was 216 patients (108 in each group).

Considering the possibility that the target sample size would not have been reached, we anticipated that the total sample size at the end of the enrolment period would have been around 100 patients. With such a total sample size, CHAT achieves 80% power to detect a difference of 20% between the two withdrawal proportions (25% in the group treated with clozapine plus haloperidol versus 5% in the group treated with clozapine plus aripiprazole). (fig.1)

The sample size calculation was performed using PASS software (Hintze, 2004).

Figure 1. Study potency



Random Allocation Procedure

Patients were randomly assigned to one of the two treatment groups with an equal probability of assignment to each treatment (allocation ratio 1:1).

A centralised randomization procedure was employed. The trial biostatistician prepared the sequence of treatments randomly permuted in blocks of constant size. The site investigators did not know the block size.

The allocation was stratified by living condition (residential facility versus all the other living conditions) because in patients with resistant schizophrenia this hard variable may be considered a proxy of severity of illness.

The randomization schedule was generated using STATA software 8 (StataCorp, College Station, TX, USA).

Recruiting physicians were asked to contact an operator at the World Health Organisation Collaborative Centre of the University of Verona. The operator had access to a computerised system that provided, after information on the enrolled participant was entered, the patient's identification number (ID) and the allocated treatment. The operator had not access to the randomisation lists.

This procedure of randomisation was developed to fully conceal treatment allocation (Altman and Schulz, 2001).

Statistical consideration

The statistical analysis was masked, i.e. the trial biostatistician was blinded to the treatment groups until the analysis had been completed. Moreover, the trial biostatistician was not involved in determining patients' eligibility, in administering the treatment, in measuring the outcomes or in entering data.

Two data locks occurred during the study. The first one happened 3 months after the end of the enrolment period, when the information on the primary endpoint

and on the short-term secondary endpoints were available for all the participants. The second one happened at the end of the study (12 months after the end of the enrolment period), when information on the long-term secondary endpoints were available for all participants. Accordingly, two data analyses were performed on an intention-to-treat (ITT) basis. All randomised participants who received at least one dose of the investigational drugs will be were included in the ITT analysis.

Statistical analysis

All randomised participants who received at least one dose of the investigational drugs were included in the intention-to-treat (ITT) analysis of the primary outcome. The distribution of the socio-demographic, biometric, functional and clinical characteristics of the patients evaluated at baseline, and drugs utilization in the past and at randomization, were compared with the Pearson's chi-squared test, the Fisher's exact test, the Student's t-test and the Wilcoxon rank-sum test, as appropriate. No correction for multiple testing was performed.

The BPRS total score (at baseline and at month 3) was computed as the sum of the scores obtained from the 24 items measuring positive/negative symptoms, depression/anxiety and disorganization. The LUNSERS total score (at baseline and at month 3) was computed as the sum of the scores obtained from the 39 and 41 items for males and females, respectively, covering psychological, neurological, autonomic, hormonal and other miscellaneous side-effects, whereas the 10 "red herring" items were not considered. In case of missing information, both the BPRS and LUNSERS total scores were computed multiplying the mean score obtained from the observed items by the total number of items (e.g. the LUNSERS total score for a male with k non-missing items is: [sum of the observed scores / k] * 39).

The proportion of patients withdrawing from the allocated treatment within three months (primary outcome) was compared between the two groups of treatment by the Person's chi-squared test, whereas the risk ratio was calculated using a Poisson regression model with a robust standard error (obtained by the Huber / White / sandwich estimator of the variance) and no offset (Zou, 2004). The change in severity of illness (measured by the BPRS total score) and the change in subjective tolerability of antipsychotic drugs (measured by the LUNSERS total score) from baseline to month 3 were compared between the two groups of treatment by the analysis of covariance with the value at baseline as a covariate and robust standard errors.

A multivariable analysis was performed to compare the differential efficacy/tolerability of the two treatments adjusting for the potential confounding effect of the main prognostic factors measured at baseline (sex, age, living condition, BPRS and LUNSERS total scores), and to test the interaction between each prognostic factor and the allocated treatment. Poisson and linear regression models with robust standard errors (obtained by the Huber / White / sandwich estimator of the variance) and no offset were used (Zou, 2004).

The statistical analysis was performed using STATA software 10 (StataCorp, College Station, TX, USA).

4 OUTCOMES

Withdrawal from allocated treatment within three months was the primary outcome. This outcome was selected because stopping or changing antipsychotic combination treatment is a frequent occurrence and major problem in the treatment of patients with schizophrenia.

Pragmatically, combination treatment was considered withdrawn if:

- clozapine was continued and the allocated treatment stopped;
- clozapine was stopped and the allocated treatment continued;
- both clozapine and the allocated treatment were stopped;
- other antipsychotic drugs were added on a regular basis to the allocated combination treatment.
- Combination treatment was not considered withdrawn if:
    - other antipsychotic drugs were occasionally administered for emergency purposes (e.g., parenteral antipsychotic drug administration during Accident & Emergency admission);
    - antipsychotic treatment was temporarily stopped (for no more than two weeks in six months) for reasons not related to clinical status.

Severity of illness was measured by means of the BPRS 24 (Ruggeri *et al.* 2005), and the perspective of patients exposed to antipsychotic agents by means of the LUNSERS (Morrison *et al.* 2000).

5 RESULTS

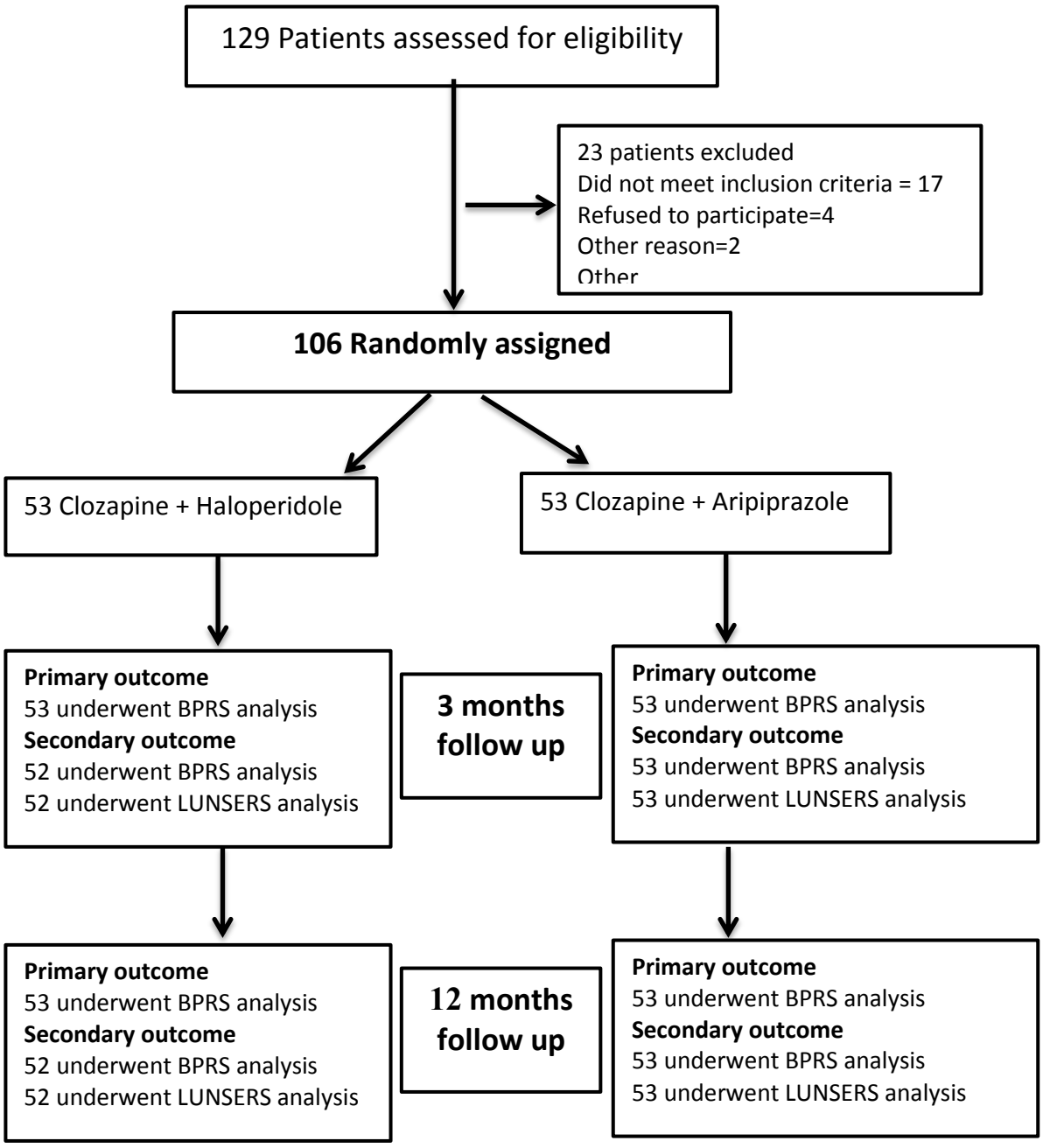
Characteristics and disposition of patients

A total of 59 Italian centers took part to the study. (Figure 2).

Figure 3 depicts the enrollment, randomization and follow-up of study patients. Of 129 patients screened for inclusion, 106 were enrolled in the study and randomly assigned to treatment. With such a total sample size, the study had 85% power to detect a 20% difference in the proportion that discontinued the two assigned treatments (25% in the group treated with clozapine plus haloperidol versus 5% in the group treated with clozapine plus aripiprazole). All 106 patients constituted the ITT population for the primary outcome. No patients were lost to follow-up, although the BPRS and LUNSERS were not completed at month 3 for one patient, who was excluded from the analysis of these continuous outcomes. Table 2 shows the baseline demographic and clinical characteristics of the patients. The majority of patients were males, with a mean age of 40.3 and 41.5 years in the aripiprazole and haloperidol groups, respectively; 35.8 and 34.0% were living in psychiatric residential facilities, and the median disease duration was 14 and 18 years in the aripiprazole and haloperidol groups, respectively. All patients had a diagnosis of schizophrenia at the MINI interview, and 26.4% in the aripiprazole group and 34.0% in the haloperidol group had a positive history for alcohol abuse. At baseline, patients had been receiving clozapine for 3.9 and 5.0 years in the aripiprazole and haloperidol group, respectively. The great majority of patients had already received haloperidol in the past, while only a minority had received aripiprazole in the past.

Figure 2. Recruiting Centers

Figure 3. Flow chart of the study CHAT.



Effectiveness and tolerability measures

After three months, the analysis of the primary outcome revealed no difference in the proportion of patients who discontinued treatment between the aripiprazole and haloperidol groups (13.2 vs 15.1%, p = 0.780) (Table 3).

Combination treatment was discontinued in 7 patients allocated to the aripiprazole group (4 patients discontinued aripiprazole and continued with clozapine monotherapy, 1 patients discontinued both aripiprazole and clozapine and started fluphenazine, and 2 patients interrupted aripiprazole for more than 15 days) and in 8 patients allocated to the haloperidol group (5 patients discontinued haloperidol and continued with clozapine monotherapy, 1 patient discontinued haloperidol and added aripiprazole, 1 patient discontinued haloperidol and received clozapine combined with olanzapine and clotiapine, and 1 patient was given clotiapine in addition to clozapine and haloperidol).

Drug use at month 3 according to the allocated treatment is presented in Table 4. The mean daily dose of clozapine was 421 and 395 mg in the aripiprazole and haloperidol group, respectively. Aripiprazole was administered at a mean daily dose of 11.8 mg, and haloperidol was administered at a mean daily dose of 2.8 mg. There was no difference in the use of concomitant medications between the two groups.

The 3-month change of the BPRS total score (ΔBPRS) was similar in the aripiprazole and haloperidol groups (-5.9 vs -4.4 points, p = 0.523), while the 3-month decrease of the LUNSERS total score (ΔLUNSERS) was significantly higher in the aripiprazole group than in the haloperidol group (-7.4 vs -2.0 points, p = 0.006) after adjusting for the baseline value (Table 3). The differential ΔLUNSERS in the aripiprazole and haloperidol groups was confirmed when the

14 subjects with at least one missing item in the LUNSERS total score at baseline and/or at month 3 were excluded from the analysis (-7.2 vs -1.8 points, p = 0.012). After twelve months, the analysis of the primary outcome revealed no difference in the proportion of patients who discontinued treatment between the aripiprazole and haloperidol groups (30.8 vs 38.0%, p = 0.442) (Table 4). The 12-month change of the BPRS total score (ΔBPRS) was similar in the aripiprazole and haloperidol groups (-7.0 vs -7.7 points, p = 0.801), while the 12-month decrease of the LUNSERS total score (ΔLUNSERS) was only slightly higher in the aripiprazole group than in the haloperidol group (-7.0 vs -2.3 points, p = 0.085) after adjusting for the baseline value (Table 5).

Multivariable analysis

The comparison of the efficacy/tolerability between aripiprazole and haloperidol adjusted for the prognostic factors measured at baseline provided the same results as those obtained in the main analysis (Table 6). The differential ΔLUNSERS between the allocated treatments (beta regression coefficient (β) = difference between the adjusted mean ΔLUNSERS in the aripiprazole group and the adjusted mean ΔLUNSERS in the haloperidol group = -5.4 points, 95% CI: -9.4 to -1.5) was confirmed when the 14 subjects with at least one missing item in the LUNSERS total score at baseline and/or at month 3 were excluded from the analysis (β = -5.5 points, 95% CI: -9.9 to -1.2).

Female sex (risk ratio (RR) = 3.60, 95%CI: 1.44 to 8.98) and younger age (RR = 0.72, 95%CI: 0.59 to 0.88, for a 5-year increase of age at baseline) were both associated with a higher risk of treatment withdrawal. Additionally, a higher LUNSERS total score at baseline was positively associated with the primary

outcome (RR = 1.11, 95% CI: 1.00 to 1.23, for a 5-point increase of the score at baseline), even if this relationship did not reach the statistical significance (p = 0.051).

Higher values of the BPRS total score at baseline were significantly associated with a greater 3-month decrease of the BPRS total score (β = ΔBPRS for a 5-point increase of the score at baseline = -1.1 points, 95% CI: -1.9 to -0.4).

The negative association between the BPRS total score at baseline and ΔBPRS was confirmed when the 12 subjects with at least one missing item in the BPRS total score at baseline and/or at month 3 were excluded from the analysis (β = -1.4 points, 95% CI: -2.1 to -0.7).

A statistically significant interaction (p = 0.011) was found between the allocated treatments, the LUNSERS total score at baseline and ΔLUNSERS. In particular, a 3-month decrease of the LUNSERS total score was found only among the patients in the aripiprazole group (β = ΔLUNSERS for a 5-point increase of the score at baseline = -2.3 points, 95% CI: -3.1 to -1.4).

The negative association between the LUNSERS total score at baseline and ΔLUNSERS in the aripiprazole group was confirmed when the 14 subjects with at least one missing item in the LUNSERS total score at baseline and/or at month 3 were excluded from the analysis (β = -2.4 points, 95% CI: -3.3 to -1.5).

6 DISCUSSION

In the present randomized trial two clozapine combination strategies were compared in a representative sample of patients with treatment-resistant schizophrenia. In terms of treatment discontinuation and psychotic symptoms, clozapine combined with aripiprazole provided no additional benefit in comparison with clozapine combined with haloperidol.

By contrast, in terms of tolerability, the addition of aripiprazole was associated with better patient perception of adverse effects.

The background logic that guided the development of the present study was based on the need to provide real-world suggestions for patients who do not have an optimal response to clozapine and for whom clinicians feel the pressing need to add a second antipsychotic drug.

We made the choice of comparing two active clozapine combination strategies, without a placebo arm, as we reasoned that clinicians would have been reluctant to accept the possibility of allocating such difficult-to-treat-patients to placebo. The choice of haloperidol was determined by prevailing clinical practice, and we designed the trial so that it would not interfere with the routine care of participants: eligibility criteria were simple, doses of the experimental drugs and concomitant medications were at the discretion of the attending doctor, and data collection was minimised. Besides, the primary outcome was treatment discontinuation, a measure that integrates patients' and clinicians' judgments of efficacy, safety, and tolerability into a global measure of effectiveness that reflects their evaluation of therapeutic benefits in relation to undesirable effects (Lieberman *et al.* 2005).

Likely, the open-label design employed in this trial has increased its external validity and generalizability (Cipriani *et al.* 2009d; Rendell *et al.* 2004).

Lack of improvement with the addition of aripiprazole compared to the addition of haloperidol is in line with the similarly negative studies of previous studies of augmentation of clozapine with various antipsychotics (Barbui *et al.* 2009b; Cipriani *et al.* 2009b).

The only randomized comparison that involved aripiprazole, carried out by Chang and colleagues, included 62 patients assigned to aripiprazole or placebo (Chang *et al.* 2008). After 8 weeks of double-blind treatment, aripiprazole augmentation of clozapine did not lead to a significant improvement of total symptom severity, but a favorable change in some adverse effects, including prolactin and triglyceride levels, was observed.

In the present study we described adverse effects employing the patient viewpoint and, consistently with Chang and colleagues, it was found that the addition of aripiprazole was associated with a better perception of adverse effects. Observational case series of patients exposed to clozapine plus aripiprazole similarly suggested improvements in adverse effects, possibly mediated by a decrease in clozapine dose when compared with aripiprazole (Mule *et al.* 2008).

In the present study, a negligible decrease in clozapine dosages was observed at follow-up in the aripiprazole group, while aripiprazole dose was similar to that recorded in the Chang and colleagues study (Chang *et al.* 2008). It is therefore possible the better perception of aripiprazole might be related to how this antipsychotic compares with haloperidol and not to the dose regimen of clozapine.

At the time that CHAT was designed, the CATIE trial was the only randomized study that employed treatment withdrawal as primary outcome measure. Subsequently, the results of the EUFEST study were published (Kahn *et al.* 2008b).

The EUFEST study was an open randomized controlled trial of haloperidol versus second-generation antipsychotic drugs in patients with schizophrenia aged 18-40 years. In this study the primary outcome measure was all-cause treatment discontinuation. In contrast with the CATIE trial, and similarly to the CHAT, the EUFEST study employed treatment discontinuation as primary outcome with an open study design, in which patients knew which medication they were taking. In the EUFEST study a compelling discrepancy was found between treatment discontinuation, that was in favor of second-generation antipsychotics, and symptom scores measured using a rating scale administered under blind conditions, that found no differences between competitive treatments (Kahn *et al.* 2008b). The authors hypothesized that expectations of psychiatrists could have led to haloperidol being discontinued more often, thus casting doubts on the use of treatment discontinuation under open conditions. We note that in the CHAT study no discrepancy between the primary outcome measure, recorded under open conditions, and symptom scores, recorded by blind staff, was observed. We therefore believe that the pragmatic design of the present study, including lack of blindness, should not have hampered the analysis of the main outcomes, considering that the design was based on a comparison of two active interventions, and doctors used to have no a priori expectations of which intervention would be better.

Another issue is whether the open design of CHAT affected the ratings at the LUNSERS, considering that this scale was self-rated by patients who knew their drug assignment.

We cannot rule out the possibility that expectations of patients led to haloperidol being systematically rated as more troublesome than aripiprazole, although we note that no association between LUNSERS ratings and antipsychotic drug

treatment (first versus second generation) was found in a recent multicentre study conducted in four European countries (Barbui *et al.* 2005). It is therefore reasonable to assume that patients had no a priori expectations of which intervention would be better tolerated. Additionally, if patients had had strong a priori expectations against haloperidol then they would not have consented to be randomly included in a study with 50% of possibilities to receive haloperidol.

The main limitation of this study is that we failed to reach the target sample size.

Although CHAT is the largest randomized comparison so far carried out in a Western country in this difficult-to-treat population, the confidence interval around the risk ratio point estimate ranges from the possibility that aripiprazole is appreciably better than haloperidol to the possibility that haloperidol is appreciably better than aripiprazole.

Another potential weakness is that lack of blindness leaves the possibility of performance bias, that is investigators and participants might have behaved systematically differently dependent on the allocated treatment. Although we cannot completely rule out this possibility, we note that the involvement of many recruiting sites and many investigators should have diluted this possibility, making very unlikely that in different sites different investigators systematically behaved differently dependent on the allocated treatment. The observed lack of difference in the primary outcome seems to provide further indirect evidence against the possibility of performance bias.

The multivariable analysis further reinforced the relationship between allocated treatment and perception of adverse effects: having adjusted for possible confounders, clozapine plus aripiprazole was associated with a higher 3-month decrease of the LUNSERS score as compared to clozapine plus haloperidol.

Additionally, female sex, young age, and negative perception of adverse effects were independent prognostic factors of the risk of withdrawal within three months. This is in line with epidemiological data suggesting that, in real world settings, age, gender and adverse effects are associated with treatment adherence, including adherence to antipsychotic drug treatment (Nose *et al.* 2003). Young age is associated with lower illness insight, and therefore it is possible that young people may be more reluctant to adhere to antipsychotic drug treatment, especially when two agents are prescribed concurrently. Moreover, women perceive antipsychotic drugs as less tolerable than men (Barbui *et al.* 2005), and therefore the relationship between female gender and treatment discontinuation might be mediated by poor tolerability.

In conclusion, the results of this study indicate that augmentation of clozapine with aripiprazole offers no benefit with regard to treatment withdrawal and overall symptoms in schizophrenia as compared with augmentation with haloperidol. However, the favorable advantage in the perception of adverse effects with aripiprazole treatment is encouraging. This finding needs to be replicated by additional randomized and observational studies that, ideally, should include a formal cost-effectiveness analysis that takes into consideration drug acquisition costs.

Table 2. Baseline characteristics of the patients according to the allocated treatment.

	CLOZAPINE and HALOPERIDOL		CLOZAPINE and ARIPIPRAZOLE		
	n	**% / mean / median**	**n**	**% / mean / median**	**p-value***
Females (%)	53	32.1	53	37.7	0.541
Age (years), mean (sd)	53	41.5 (9.4)	53	40.3 (10.3)	0.549
High school diploma or academic degree (%)	53	35.8	51	41.2	0.577
Occupational status (%)					
employed / sheltered employed, house-person, student	51	33.3	52	28.8	0.846
unemployed		17.7		21.2	
retired		49.0		50.0	
Living in residential facility in the past six months (%)	53	34.0	53	35.8	0.839
Length of stay in residential facility[†] (years), median (IQR)	15	2.7 (1.3-3.9)	14	3.2 (1.2-6.5)	0.513
Living status (%)					
alone		7.7		9.6	
with relatives	52	53.9	52	53.9	0.138
with other patients		28.8		36.5	
other		9.6		0.0	
Diagnosis of schizophrenia (MINI criteria) (%)	53	100.0	53	100.0	-
Disease duration (years), median (IQR)	52	18 (12-24)	52	14 (8-20)	0.076
Number of hospital admissions during lifetime, median (IQR)	53	5 (1-10)	53	3 (1-8)	0.428
BPRS total score, median (IQR)	53	60 (52-79)	53	60 (52-71)	0.395

	CLOZAPINE and HALOPERIDOL		CLOZAPINE and ARIPIPRAZOLE		
	n	**% / mean / median**	**n**	**% / mean / median**	**p-value***
Systolic blood pressure (mmHg), mean (sd)	48	124.7 (12.4)	49	122.3 (13.6)	0.361
Diastolic blood pressure (mmHg), mean (sd)	48	81.4 (8.7)	49	77.8 (8.7)	0.041
Body Mass Index (kg/m^2), median (IQR)	48	26.8 (24.7-31.2)	45	25.9 (24.7-28.7)	0.389
Electrocardiographic anomalies (%)	45	20.0	46	8.7	0.123
Electroencephalographic anomalies (%)	42	11.9	40	7.5	0.713
Mental retardation (%)					
absent	53	94.3	53	94.3	1.000
mild		5.7		5.7	
moderate / severe		0.0		0.0	
Cognitive degradation (%)					
absent		94.3		85.0	
mild	53	3.8	53	7.5	0.318
moderate		1.9		7.5	
severe		0.0		0.0	
Current alcohol abuse (%)	53	0.0	52	0.0	-
History of alcohol abuse (%)	53	34.0	53	26.4	0.397
History of self-harm behaviour (%)	53	18.9	52	11.5	0.296
History of suicidal attempts (%)	53	20.8	51	11.8	0.215
History of epilepsy (%)	51	7.8	53	3.8	0.432
History of tardive dyskinesia (%)	53	7.5	52	5.8	1.000

	CLOZAPINE and HALOPERIDOL		CLOZAPINE and ARIPIPRAZOLE		
	n	**% / mean / median**	**n**	**% / mean / median**	**p-value***
Past use of clozapine					
length (years), median (IQR)	53	5.0 (1.8-8.6)	52	3.9 (1.7-8.2)	0.524
max dose (mg/die), mean (sd)	52	483 (158)	51	452 (118)	0.266
Past use of haloperidol (%)	53	88.7	52	76.9	0.110
Past use of aripiprazole (%)	53	3.8	52	9.6	0.270
Past use of other antipsychotics (%)	53	94.3	52	92.3	0.716
Past use of new antipsychotics‡ (%)	53	73.6	52	76.9	0.692
Past use of depot antipsychotics (%)	53	15.1	53	13.2	0.780
Dose of clozapine (mg/die) at baseline, mean (sd)	53	413 (157)	53	418 (141)	0.871
Dose of haloperidol (mg/die) at baseline, mean (sd)	53	2.1 (1.3)	-	-	-
Dose of aripiprazole (mg/die) at baseline, mean (sd)	-	-	53	8.7 (3.9)	-
Use of other drugs at baseline (%)	53	67.9	53	77.4	0.276
antidepressants		18.9		24.5	
benzodiazepines		62.3		69.8	
mood stabilizers		18.9		9.4	
Use of anticholinergics at baseline (%)	53	0.0	53	1.9	1.000
LUNSERS total score, median (IQR)	53	22 (16-32)	53	23 (16-32)	0.791

sd: standard deviation, IQR: interquartile range

* obtained by the Pearson's chi-squared test, the Fisher's exact test, the Student's t-test or the Wilcoxon rank-sum test

† only for the 18 and 19 patients allocated to clozapine and haloperidol, and to clozapine and aripiprazole, respectively, who reported a stay in a residential facility in the past 6 months

‡ risperdal, clozapine, olanzapine, quetiapine, zotepine, ziprasidone, aripiprazole or amilsulpiride

Table 3. Withdrawal from the allocated treatment within three months (primary outcome), change in the BPRS total score (ΔBPRS) and change in the LUNSERS total score (ΔLUNSERS) from baseline to month 3. Comparison between the allocated treatments (reference group: clozapine and haloperidol).

	CLOZAPINE and HALOPERIDOL	**CLOZAPINE and ARIPIPRAZOLE**	**p-value**
Withdrawal from the allocated treatment			
number of patients (number of events)	53 (8)	53 (7)	
cumulative incidence (SE) [95%CI]*	15.1% (4.9%) [6.7%, 27.6%]	13.2% (4.7%) [5.5%, 25.3%]	0.780†
risk ratio (SE) [95%CI]‡	1.00	0.87 (0.42) [0.34, 2.25]	
ΔBPRS			
number of patients	52	53	
adjusted mean change¶ (SE) [95%CI]	-4.4 (1.5) [-7.5, -1.4]	-5.9 (1.7) [-9.4, -2.5]	0.523
beta regression coefficient§ (SE) [95%CI]	0.00	-1.5 (2.3) [-6.1, +3.1]	
ΔLUNSERS			
number of patients	52	53	
adjusted mean change¶ (SE) [95%CI]	-2.0 (1.4) [-4.8, +0.8]	-7.4 (1.3) [-10.0, -4.8]	0.006
beta regression coefficient§ (SE) [95%CI]	0.00	-5.4 (1.9) [-9.2, -1.5]	

SE: standard error, 95%CI: 95% confidence interval
* binomial exact confidence interval
† obtained by the Pearson's chi-squared test
‡ obtained by a Poisson regression model with a robust standard error and no offset
¶ mean ΔBPRS / ΔLUNSERS, adjusted for the baseline mean-centered value of the BPRS / LUNSERS total score by a linear regression model with robust standard errors
§ difference between the adjusted mean ΔBPRS / ΔLUNSERS among the patients allocated to clozapine and aripiprazole, and the adjusted mean ΔBPRS / ΔLUNSERS among the patients allocated to clozapine and haloperidol

Table 4. Drug use at month 3 according to the allocated treatment.

	CLOZAPINE and HALOPERIDOL		CLOZAPINE and ARIPIPRAZOLE		
	n	**% / mean**	**n**	**% / mean**	**p-value***
Dose of clozapine (mg/die) at month 3, mean (sd)	53	395 (161)	52	421 (142)	0.376
Dose of haloperidol (mg/die) at month 3, mean (sd)	46	2.8 (1.7)	-	-	-
Dose of aripiprazole (mg/die) at month 3, mean (sd)	1	15 (-)	48	11.8 (5.1)	-
Use of other drugs at month 3 (%) antidepressants benzodiazepines mood stabilizers	53	67.9 24.5 56.6 17.0	53	69.8 18.9 62.3 11.3	0.834
Use of anticholinergics at month 3 (%)	53	1.9	53	3.8	1.000

Table 5. Withdrawal from the allocated treatment within twelve months, change in the BPRS total score (ΔBPRS) and change in the LUNSERS total score (ΔLUNSERS) from baseline to month 12. Comparison between the allocated treatments (reference group: clozapine and haloperidol).

	CLOZAPINE and HALOPERIDOL	**CLOZAPINE and ARIPIPRAZOLE**	**p-value**
Withdrawal from the allocated treatment			
number of patients (number of events)	52 (16)	50 (19)	
cumulative incidence (SE) [95%CI]*	30.8% (6.4%) [18.7%, 45.1%]	38.0% (6.9%) [24.7%, 52.8%]	0.442[†]
risk ratio (SE) [95%CI][‡]	1.00	1.23 (0.34) [0.72, 2.12]	
ΔBPRS			
number of patients	51	50	
adjusted mean change[¶] (SE) [95%CI]	-7.7 (1.6) [-10.9, -4.5]	-7.0 (2.2) [-11.5, -2.5]	0.801
beta regression coefficient[§] (SE) [95%CI]	0.00	+0.7 (2.8) [-4.8, +6.2]	
ΔLUNSERS			
number of patients	51	50	
adjusted mean change[¶] (SE) [95%CI]	-2.3 (2.0) [-6.4, +1.7]	-7.0 (1.8) [-10.5, -3.5]	0.085
beta regression coefficient[§] (SE) [95%CI]	0.00	-4.7 (2.7) [-10.0, +0.7]	

SE: standard error, 95%CI: 95% confidence interval

* binomial exact confidence interval

[†] obtained by the Pearson's chi-squared test

[‡] obtained by a Poisson regression model with a robust standard error and no offset

[¶] mean ΔBPRS / ΔLUNSERS, adjusted for the baseline mean-centered value of the BPRS / LUNSERS total score by a linear regression model with robust standard errors

[§] difference between the adjusted mean ΔBPRS / ΔLUNSERS among the patients allocated to clozapine and aripiprazole, and the adjusted mean ΔBPRS / ΔLUNSERS among the patients allocated to clozapine and haloperidol

Table 6. Withdrawal from the allocated treatment within three months, change in the BPRS total score (ΔBPRS) and change in the LUNSERS total score (ΔLUNSERS) from baseline to month 3. Mutually adjusted risk ratios[†] and beta regression coefficients[‡] for the association between the allocated treatment, the main prognostic variables measured at baseline and the short-term outcomes.

	Withdrawal from the allocated treatment (n = 106)	**ΔBPRS (n = 105)**	**ΔLUNSERS (n = 105)**
	risk ratio [95%CI]	**beta regression coefficient [95%CI]**	
Allocated treatment (*cloz. and aripiprazole vs cloz. and haloperidol*)	**0.77 [0.26, 2.25]**	**-1.5 [-6.1, +3.1]**	**-5.4 [-9.4, -1.5] ***
Gender (*female vs male*)	**3.60 [1.44, 8.98] ***	**+3.3 [-1.6, +8.1]**	**-1.7 [-6.4, +2.9]**
Age[¶] (*5-year increase*)	**0.72 [0.59, 0.88] ***	**-0.1 [-1.4, +1.1]**	**+0.4 [-0.7, +1.4]**
Living condition in the past six months (*residential facility vs at home*)	**2.10 [0.89, 4.98]**	**+1.4 [-3.4, +6.3]**	**-0.9 [-5.0, +3.2]**
BPRS total score[¶] (*5-point increase*)	**1.05 [0.93, 1.20]**	**-1.1 [-1.9, -0.4] ***	**-0.1 [-0.7, +0.5]**
LUNSERS total score[¶] (*5-point increase*)	**1.11 [1.00, 1.23]**	**-0.6 [-1.5, +0.3]**	**-0.5 [-1.5, +0.5]**[§] **-2.3 [-3.1, -1.4]**[§] **
Constant		**-6.1 [-9.8, -2.3] ***	**-0.9 [-4.1, 2.2]**

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Appendice 1

Modulo di consenso informato

Luogo e data _____

Io sottoscritto/a _____ nato a _____
residente a _____ in via _____

dichiaro

di accettare la proposta di sottopormi alla sperimentazione clinica denominata CLOZAPINA E ARIPIPRAZOLO VERSO CLOZAPINA E ALOPERIDOLO NEL TRATTAMENTO DELLA SCHIZOFRENIA

Sono stato/a adeguatamente informato/a circa gli scopi dello studio e le metodiche dello stesso, in particolare sono consapevole della necessità di osservare le indicazioni e le regole che mi sono state illustrate e che ho perfettamente compreso.

Sono a conoscenza dei benefici che mi possono derivare dalla partecipazione allo studio, ma anche degli eventuali rischi e di tutti i disagi connessi.

Mi è stato spiegato che dal nuovo trattamento ci si attendono risultati migliori o comunque vantaggi rispetto ai trattamenti oggi in uso; ad ogni modo mi è stato assicurato che non subirò, prevedibilmente, alcun aggravamento delle mie condizioni cliniche né vi sarà un ritardo nei tempi solitamente necessari, in casi analoghi, per la guarigione, per la stabilizzazione della patologia o per il controllo della sintomatologia.

Sono consapevole che in qualsiasi momento potrò sospendere la sperimentazione ed esigere di essere curato/a con le terapie ordinarie per la patologia di cui soffro, senza obbligo da parte mia di motivare la decisione, a meno che la stessa non derivi dalla comparsa di disturbi o effetti indesiderati o non previsti, nel qual caso mi impegno sin da ora a comunicarne tempestivamente al medico sperimentatore natura ed entità.

Dichiaro che il mio consenso è espressione di una libera decisione, non influenzata da promesse di denaro o di altri benefici, né da obblighi di gratitudine o di amicizia e/o parentela nei confronti del medico sperimentatore.

Acconsento che le notizie riguardanti la sperimentazione, limitatamente a quelle che potrebbero rivelarsi utili ai fini della mia salute, vengano trasmesse al mio medico curante, dott. _____

Autorizzo sin d'ora l'utilizzo e la divulgazione, in forma anonima e per sole finalità scientifiche e amministrative e nell'osservanza delle vigenti norme sulla tutela della riservatezza, dei risultati della sperimentazione, compresi i dati clinici che mi riguardano.

Firma

_____

Il Medico Sperimentatore

_____

_____

(nome in stampatello)

Testimone

_____

_____

(nome in stampatello)

Allegato: n._____ fogli contenenti notizie sugli scopi, metodi, benefici attesi e rischi, connessi con la sperimentazione.

Appendice 2

Scheda di reclutamento

Numero identificativo CHAT: |___||___||___||___||___||___|

C lozapine
H aloperidol
A ripiprazole
T rial

Iniziali del paziente (nome e cognome): |___||___||___|

Data di nascita: __ /__ /_____ **Sesso:** (M) (F)

Nome del medico: ..... **Data della compilazione:** __ /__ /_____

Centro reclutante: .....

SCHEDA 1 - RECLUTAMENTO

DA COMPILARE DA PARTE DEL MEDICO

A. CRITERI GENERALI di INCLUSIONE nello STUDIO

(?) **Il paziente ha una diagnosi clinica di schizofrenia?** SI'

(?) **Il paziente è in trattamento con clozapina da almeno 6 mesi, ad una dose di almeno 400 mg/die (o dosi minori, a causa di effetti collaterali)?** SI'

(?) **Persistono sintomi positivi (deliri/allucinazioni, disorganizzazione)?** SI'

(?) **Il paziente ha compiuto 18 anni e risiede stabilmente in Italia?** SI'

(?) **Il paziente ha firmato il consenso informato?** SI'

Se si risponde SI' a tutte le domande, procedere con la compilazione della scheda come segue

ASPETTI CLINICI RILEVANTI PRESENTI AL RECLUTAMENTO

(barrare una o più opzioni)

Tentativi di fuga	☐	Rischio di suicidio	☐
Autolesionismo	☐	Alcolismo	☐
Aggressività	☐	Deliri/allucinazioni, disorganizzazione	☐
Distruttività verso le cose	☐	Appiattimento affettivo, abulia/alogia	☐
Nessun problema	☐	Altro	☐

B. NOTIZIE SOCIO-DEMOGRAFICHE e SALUTE FISICA

Stato civile |___| *1=celibe/nubile; 2=coniugato/a, convivente; 3=separato/a; 4=vedovo/a; 5=libero/a di stato*

Scolarità |___| *1=analfabeta; 2=alfabetizzato senza titolo di studio; 3=licenza elementare; 4=diploma media inferiore; 5=diploma media superiore /laurea*

Lavoro |___| *1=occupato; 2=disoccupato in cerca di nuova occupazione;3=in cerca di prima occupazione; 4=casalinga; 5=studente; 6=ritirato dal lavoro o pensionato; 7=altra condizione (lavoro protetto)*

(?) **DOVE viene reclutato il paziente?**

|___| *1=in SPDC; 2=in ambulatorio; 3=in struttura residenziale **senza operatore**; 4=In struttura residenziale **con operatore (< 12 h/die)**; 5=In struttura residenziale **con operatore (> 12 h/die)**; 6=altro.....*

(?) **Negli ultimi 6 mesi DOVE ha vissuto il paziente?**

|___| *1=in SPDC; 2=a casa; ; 3=in struttura residenziale **senza operatore**; 4=In struttura residenziale **con operatore (< 12 h/die)**; 5=In struttura residenziale **con operatore (> 12 h/die)**; 6=altro.....*

Se in struttura residenziale, riportare da quando* (mese e anno)? |___|___| |___|___|___|___|
** Inserire la data del primo inserimento assoluto in struttura residenziale (inizio del percorso riabilitativo)*

(?) **CON CHI vive il paziente?** |___|

1=da solo; 2=con familiari; 3=con altri pazienti; 4=altro.....

(?) **Esce** di propria iniziativa? |___|

1=tutti i giorni; 2=più volte/settimana; 3=più volte/mese; 4=meno di 1 volta /mese; 5=mai

(?) Le **uscite** di propria iniziativa avvengono

|___| *1=abitualmente senza operatori; 2=abitualmente accompagnato da operatori*

Il paziente soffre **attualmente** di dipendenza/abuso da sostanze/alcol? ▫ **SI'** ▫ **NO**

Il paziente **in passato** ha sofferto di dipendenza/abuso da sostanze/alcol? ▫ **SI'** ▫ **NO**

Storia di epilessia? ▫ **SI'** ▫ **NO**

Ritardo mentale? ▫ **No** ▫ **Lieve** ▫ **Moderato** ▫ **Grave**

Deterioramento cognitivo su base organica? ▫ **No** ▫ **Lieve** ▫ **Moderato** ▫ **Grave**

Altre malattie organiche concomitanti? ▫ **SI'** ▫ **NO**

Se sì, indicare quali:

1._____ 2._____ 3._____

(?) **Pressione arteriosa** (oggi) ..... / ..... (?) **Peso corporeo** (oggi) ..... Kg

(?) **Circonferenza addominale** (oggi) ..... cm (?) **Altezza** ..... cm

ALLEGARE FOTOCOPIA dei più recenti esami del sangue effettuati, avendo cura di inserire, se possibile, emocromo con formula, trigliceridi, colesterolo tot. e HDL, glicemia e prolattina

(?) **Vi sono anomalie elettrocardiografiche** (ECG)? ▫ **SI'** ▫ **NO**

Vi sono anomalie elettroencefalografiche (EEG)? ▫ **SI'** ▫ **NO**

Se SI' e se possibile, specificare quali o allegare referto .....

.....

C. NOTIZIE CLINICHE

Data del primo contatto psichiatrico assoluto (anno) |___|___|___|___|

Numero **approssimativo** di ricoveri in SPDC/CSM 24h/altre strutture per acuzie |___|___|

(?) **Elenco dei <u>farmaci ANTIPSICOTICI</u> assunti <u>in passato</u>** *(barrare una o più opzioni)*

Aloperidolo	Amisulpiride
☐ Clorpromazina	☐ Aripiprazolo
Clotiapina	Olanzapina
Sulpiride	Quetiapina
☐ Promazina	☐ Risperidone
.....	.....
.....	.....

(?) Data di **inizio della terapia con clozapina** (mese/anno) |___|___| |___|___|___|___|

(?) **Massimo dosaggio di clozapina** assunto in passato? .....

Se possibile, riportare il motivo dell'eventuale riduzione del dosaggio apportata in seguito:

.....

(?) **Interventi <u>non farmacologici</u> attualmente effettuati** *(barrare una o più opzioni)*

- ☐ Psicoterapia strutturata (cognitiva, comportamentale, sistemica, altro)
- ☐ Colloqui di supporto psicologico (ogni _____ giorni circa)
- ☐ Colloquio psichiatrico
- ☐ Colloqui periodici con familiari
- ☐ Colloqui saltuari con familiari
- ☐ Riabilitazione (frequenza regolare presso CSM, gruppi di auto-aiuto, altro)
- ☐ Altri interventi .....
- ☐ Nessuno

(?) **In anamnesi si sono verificati gesti autolesivi?** **SI'** **NO**

Se sì, indicare quali: .....

(?) **In anamnesi si sono verificati tentativi di suicidio?** **SI'** **NO**

Se sì, indicare quante volte (più o meno):.....

(?) **Il paziente soffre o ha sofferto di discinesia tardiva?** **SI'** **NO**

(?) **Il paziente era in trattamento con *depot* prima dell'inserimento nello studio?**

SI' **NO**

Se sì, indicare data dell'ultima somministrazione: __ /__ /_____

(?) **Stima indicativa della adesione ("*compliance*") del paziente alla terapia**

nulla scarsa soddisfacente ottima

BRIEF PSYCHIATRIC RATING SCALE (BPRS)

1 = Non presente **3 = Lieve** **5 = Moderatamente grave** **7 = Molto grave**
2 = Molto lieve **4 = Moderato** **6 = Grave** **8 = Non valutato**

1. PREOCCUPAZIONI SOMATICHE	|___|	13. TRASCURATEZZA DELLA CURA DI SÉ	|___|
2. ANSIA	|___|	14. DISORIENTAMENTO	|___|
3. DEPRESSIONE	|___|	15. DISORGANIZZAZIONE CONCETTUALE	|___|
4. RISCHIO DI SUICIDIO	|___|	16. APPIATTIMENTO AFFETTIVO	|___|
5. SENTIMENTI DI COLPA	|___|	17. ISOLAMENTO EMOTIVO	|___|
6. OSTILITÀ	|___|	18. RALLENTAMENTO MOTORIO	|___|
7. ELEVAZIONE DEL TONO DELL'UMORE	|___|	19. TENSIONE MOTORIA	|___|
8. GRANDIOSITA'	|___|	20. MANCANZA DI COOPERAZIONE	|___|
9. SOSPETTOSITA'	|___|	21. ECCITAMENTO	|___|
10. ALLUCINAZIONI	|___|	22. DISTRAIBILITA'	|___|
11. CONTENUTO INSOLITO DEL PENSIERO	|___|	23. IPERATTIVITÀ MOTORIA	|___|
12. COMPORTAMENTO BIZZARRO	|___|	24. MANIERISMI E POSTURE	|___|

Note:

.....

.....

.....

.....

Per codificare la maggior parte degli item della BPRS si deve tener conto sia della frequenza sia della gravità dei sintomi. Può talvolta capitare che frequenza e gravità non corrispondano. In questi casi si suggerisce di utilizzare il principio gerarchico, cioè di assegnare il punteggio più elevato, sia che corrisponda alla frequenza, sia che corrisponda alla gravità. Allo stesso modo, quando la definizione operativa contiene un "E/O", al paziente dovrebbe essere assegnato il punteggio più alto delle due alternative. Per esempio, se un paziente presenta allucinazioni persistenti per tutto il giorno (punteggio 7), ma le allucinazioni interferiscono solo in maniera limitata con il funzionamento del paziente stesso (punteggio 5), il valutatore dovrebbe comunque dare il punteggio 7.
Quando non si riesce a risolvere le contraddizioni tra ciò che il paziente dice e ciò che si viene a sapere dalle altre fonti di informazione, bisogna far ricorso al proprio giudizio clinico e dare fiducia alla fonte che si considera più attendibile. Si raccomanda di prendere nota sul modulo di codifica della BPRS di queste contraddizioni e di precisare perché si è scelto quel particolare punteggio.

Frequenza dei sintomi
Le espressioni *raramente*, *talvolta*, *spesso*, possono essere interpretate in modo differente dai diversi intervistatori. Si suggerisce di adottare i riferimenti seguenti, ricordando comunque che per scegliere il livello di gravità di un sintomo occorre tener presente non solo la frequenza e la durata, ma anche l'intensità:

- *raramente, occasionalmente, occasionale o raro*:
  durata: meno del 10% del tempo nel periodo di riferimento;
  frequenza di episodi in un periodo di riferimento di un mese: 1 o 2 manifestazioni;
- *talvolta, alcuni/e*:
  durata: meno del 25% del tempo nel periodo di riferimento;
  frequenza di episodi in un periodo di riferimento di un mese: presenza in 3-7 giorni;
- *spesso, frequentemente, molti*:
  durata: 25-50% del tempo nel periodo di riferimento;
  frequenza di episodi in un periodo di riferimento di un mese: presenza in 8-14 giorni;
- *molto spesso, molto frequentemente, quasi sempre, molto frequenti*:
  durata: più del 50% del tempo nel periodo di riferimento;
  frequenza di episodi in un periodo di riferimento di un mese: presenza in 15 o più giorni.

Domande da porre al paziente

Le è mai capitato di credere che qualcuno la stava spiando o stava complottando contro di lei o cercava di danneggiarla?	☐ SI'	☐ NO
Le è mai capitato di credere che qualcuno le leggeva nel pensiero o poteva udire i suoi pensieri o che lei poteva leggere il pensiero degli altri o udire i pensieri degli altri?	☐ SI'	☐ NO
Le è mai capitato che qualcuno o qualche forza esterna potesse inserire nella sua mente pensieri non suoi, o costringerla ad agire in un modo diverso dal suo solito? Ha mai sentito di essere posseduto dal demonio?	☐ SI'	☐ NO
Le è mai capitato di credere che le venivano inviati messaggi particolari attraverso la TV, la radio o i giornali o di credere che persone che lei non conosceva personalmente fossero interessate a lei in maniera particolare?	☐ SI'	☐ NO
I suoi familiari o i suoi amici hanno mai considerato qualche sua idea o convinzione strana o insolita? Per esempio, ha mai sentito di essere posseduto dal demonio?	☐ SI'	☐ NO
Le è mai capitato di udire cose che gli altri non potevano udire come, ad esempio, delle voci? Ha mai udito una voce che commentava i suoi pensieri o il suo comportamento, o ha mai udito due o più voci che parlavano tra di loro?	☐ SI'	☐ NO
Le è mai capitato, da sveglio, di avere visioni o di vedere cose che gli altri non potevano vedere?	☐ SI'	☐ NO

Domande per il medico

Attualmente il paziente presenta incoerenza, linguaggio disorganizzato o un evidente allentamento dei nessi associativi?	☐ SI'	☐ NO
Attualmente il paziente presenta un comportamento disorganizzato o catatonico?	☐ SI'	☐ NO
Durante l'intervista prevalgono i sintomi negativi della schizofrenia, per esempio, importante appiattimento affettivo, povertà di linguaggio (alogia) o un'incapacità di iniziare o di portare a termine attività finalizzate (abulia)?	☐ SI'	☐ NO
Il paziente presenta difficoltà di funzionamento o è stato trattato o ricoverato per la presenza di sintomi psicotici?	☐ SI'	☐ NO
In base alla propria esperienza, la difficoltà di funzionamento dovuta ai sintomi psicotici può essere considerata da moderata a grave?	☐ SI'	☐ NO
La durata totale della psicosi è stata superiore ai 6 mesi?	☐ SI'	☐ NO
Il paziente soddisfa i criteri per un episodio depressivo maggiore o maniacale/ipomaniacale attuale o in anamnesi?	☐ SI'	☐ NO

Dopo aver compilato la "Scheda 1 – Reclutamento", procedere come segue:

? **Assieme alla clozapina, un trattamento in combinazione con aloperidolo o aripiprazolo è clinicamente ragionevole?**

(considerando la necessità di sospendere tutti gli altri antipsicotici, inclusi i depot e fatta eccezione per la clozapina)

SI' → **Coorte RANDOMIZZATA**

NO → **Coorte OSSERVAZIONALE**

TELEFONARE (orario ufficio)

al numero 349 6580119

per inserire il paziente nella coorte randomizzata, cioè per conoscere quale trattamento dovrà essere aggiunto alla clozapina, compilare la scheda farmaci al reclutamento e spedire tutte le schede e il consenso informato firmato via fax al Centro OMS della Università di Verona. Conservare la scheda variazioni di terapia e utilizzarla per riportare tutti i cambiamenti di terapia che verranno effettuali nei prossimi tre mesi (cioè fino al primo follow-up).

FAX: 045-585871

Le schede compilate possono essere spedite anche tramite posta elettronica all'indirizzo:

studio.chat@medicina.univr.it

TELEFONARE (orario ufficio)

al numero 349 6580119

per inserire il paziente nella coorte osservazionale, quindi compilare la scheda farmaci al reclutamento e spedire tutte le schede e il consenso informato firmato via fax al Centro OMS della Università di Verona. Conservare la scheda variazioni di terapia e utilizzarla per riportare tutti i cambiamenti di terapia che verranno effettuali nei prossimi tre mesi (cioè fino al primo follow-up).

FAX: 045-585871

Le schede compilate possono essere spedite anche tramite posta elettronica all'indirizzo:

studio.chat@medicina.univr.it

IL PAZIENTE È STATO ASSEGNATO A *(barrare una sola opzione)*:

- ☐ ***COORTE RANDOMIZZATA con ARIPIPRAZOLO***
- ☐ ***COORTE RANDOMIZZATA con ALOPERIDOLO***
- ☐ ***COORTE OSSERVAZIONALE (indicare il motivo: .....***

  .....

  .....).

Riportare la TERAPIA FARMACOLOGICA al momento dell'inizio dello studio
per tutti i pazienti inseriti sia nella coorte randomizzata sia in quella osservazionale
(PER I PAZIENTI INSERITI NELLA COORTE RANDOMIZZATA, INSERIRE IL DOSAGGIO INIZIALE IMPOSTATO E POI AGGIORNARE DI VOLTA IN VOLTA LA TERAPIA NELL'APPOSITA SCHEDA 2 – "SCHEDA VARIAZIONE TERAPIA")

DATA __ /__ /_____

Farmaco				Dose (mg/die)
Antipsicotici	CLOZAPINA	SI'		
	ALOPERIDOLO ?	SI'	NO	
	ARIPIPRAZOLO ?	SI'	NO	
Antidepressivi				
Benzodiazepine				
Stabilizzanti dell'umore				
Anticolinergici				
Altri farmaci				

In qualsiasi momento dello studio si verifichino EFFETTI COLLATERALI

COMPILARE la SCHEDA 4 – "SEGNALAZIONE DI REAZIONE AVVERSA"

DA COMPILARE DA PARTE DEL PAZIENTE
(eventualmente con l'aiuto del medico o di un operatore)

Per favore, indichi se nell'ultimo mese ha lamentato i seguenti effetti collaterali, mettendo una crocetta dove ritiene appropriato

	Assente	Poco	Abbastanza	Molto	Moltissimo
1. Eritema	☐	☐	☐	☐	☐
2. Difficoltà a stare sveglio di giorno	☐	☐	☐		
3. Naso che cola	☐	☐	☐	☐	☐
4. Aumento dei sogni	☐	☐	☐		
5. Mal di testa	☐	☐	☐		
6. Bocca secca	☐	☐	☐		
7. Gonfiore al petto	☐	☐	☐	☐	☐
8. Geloni	☐	☐	☐		
9. Difficoltà a concentrarsi	☐	☐	☐	☐	☐
10. Stitichezza	☐	☐	☐		
11. Perdita dei capelli	☐	☐	☐		
12. Urine più scure del solito	☐	☐	☐		
13. Irregolarità del ciclo	☐	☐	☐		
14. Tensione	☐	☐	☐		
15. Vertigini	☐	☐	☐	☐	☐
16. Nausea	☐	☐	☐		
17. Aumento del desiderio sessuale	☐	☐	☐		
18. Stanchezza	☐	☐	☐		
19. Rigidità muscolare	☐	☐	☐		
20. Palpitazioni	☐	☐	☐		
21. Difficoltà a ricordare le cose	☐	☐	☐	☐	☐
22. Perdita di peso	☐	☐	☐		
23. Mancanza di emozioni	☐	☐	☐		
24. Difficoltà a raggiungere l'orgasmo	☐	☐	☐		

(continua...)

(continua...)

	Assente	Poco	Abbastanza	Molto	Moltissimo
25. Fragilità delle unghie		☐			
26. Depressione	☐	☐	☐	☐	☐
27. Aumento della sudorazione		☐			
28. Ulcere in bocca	☐	☐	☐	☐	☐
29.Lentezza nei movimenti		☐			
30. Pelle grassa	☐	☐	☐	☐	☐
31. Sonnolenza		☐			
32. Difficoltà ad urinare	☐	☐	☐	☐	☐
33. Vampate al volto		☐			
34. Spasmi muscolari	☐	☐	☐	☐	☐
35. Sensibilità al sole		☐			
36. Diarrea	☐	☐	☐	☐	☐
37. Aumento della salivazione		☐			
38. Visione offuscata	☐	☐	☐	☐	☐
39. Aumento di peso		☐			
40.Irrequietezza		☐			
41. Difficoltà ad addormentarsi		☐			
42. Dolore ai muscoli del collo	☐	☐	☐	☐	☐
43. Tremori		☐			
44. Formicolii	☐	☐	☐	☐	☐
45. Dolori articolari		☐			
46. Diminuzione del desiderio sessuale		☐			
47. Macchie nuove o insolite sulla pelle		☐			
48. Movimenti involontari del corpo	☐	☐	☐	☐	☐
49. Prurito		☐			
50. Mestruazioni meno frequenti	☐	☐	☐	☐	☐
51. Aumento della quantità di urina		☐			

Appendice 3

Scheda di follow up

C lozapine
H aloperidol
A ripiprazole
T rial

Numero identificativo CHAT: |___||___||___||___||___||___|

Iniziali del paziente (nome e cognome): |___||___||___|

Data di nascita: __ /__ /_____ **Sesso:** (M) (F)

Nome del medico: ..... **Data della compilazione:** __ /__ /_____

Centro reclutante: .....

SCHEDA 3 – FOLLOW UP

DA COMPILARE DA PARTE DEL MEDICO

A. INDICATORE DI ESITO PRIMARIO

Il paziente rientra nella coorte |___| *1=randomizzata; 2=osservazionale*

Se il paziente rientra nella coorte randomizzata, compilare la sezione qui sotto riportata, altrimenti passare alla pagina successiva

Se nella coorte randomizzata, specificare il trattamento di allocazione

Clozapina + ALOPERIDOLO ☐ **Clozapina + ARIPIPRAZOLO** ☐

Dall'ultima valutazione effettuata, il trattamento combinato assegnato al momento della randomizzazione (barrare UNA SOLA OPZIONE):

☐ non è stato interrotto e non sono stati somministrati altri antipsicotici

☐ non è stato interrotto, ma sono stati somministrati occasionalmente altri antipsicotici, in totale per |___||___| giorno/i

☐ non è stato interrotto, ma sono stati aggiunti stabilmente in terapia uno o più antipsicotici

☐ è stato temporaneamente interrotto per |___||___| giorno/i

☐ è stato definitivamente interrotto il giorno __ /__ /_____ per il seguente motivo:

.....

.....

.....

.....

B. NOTIZIE CLINICHE E SALUTE FISICA

Dall'ultima valutazione, sono insorte NUOVE malattie organiche? **SI'** **NO**

Se sì, indicare quali: 1._____ 2. _____
3._____ 4. _____

Pressione arteriosa (oggi) ..... / ..... **Peso corporeo** (oggi) ..... Kg

Circonferenza addominale (oggi) ..... cm **Altezza** ..... cm

ALLEGARE FOTOCOPIA dei più recenti esami del sanque effettuati, avendo cura di inserire, se possibile, emocromo con formula, trigliceridi, colesterolo tot. e HDL, glicemia e prolattina

Vi sono anomalie elettrocardiografiche (ECG)? ▫ **SI'** ▫ **NO**
Vi sono anomalie elettroencefalografiche (EEG)? ▫ **SI'** ▫ **NO**

Se SI' e se possibile, specificare quali o allegare referto .....

.....

Dall'ultima valutazione, **ricoveri** in SPDC/CSM 24h/altre strutture per acuzie? ☐ **SI'** ☐ **NO**

Se sì, compilare la "**TABELLA RICOVERI**" qui sotto:

Data inizio	Data fine	Motivo

Interventi <u>non farmacologici</u> attualmente in corso *(barrare una o più opzioni)*

- ▫ Psicoterapia strutturata (cognitiva, comportamentale, sistemica, altro)
- ▫ Colloqui di supporto psicologico (ogni _____ giorni circa)
- ▫ Colloquio psichiatrico
- ▫ Colloqui con familiari (barrare un'opzione, se ▫ **saltuari** o ▫ **periodici**)
- ▫ Riabilitazione (frequenza regolare presso CSM, gruppi di auto-aiuto, altro)
- ▫ Altri interventi .....
- ▫ Nessuno

Dall'ultima valutazione, si sono verificati gesti autolesivi? **SI'** **NO**

Se sì, indicare quali: .....

Il paziente soffre attualmente di discinesia tardiva? **SI'** **NO**

Il paziente è in trattamento con antipsicotici *depot*? ▫ **SI'** ▫ **NO**

Se sì, indicare data dell'ultima somministrazione: __ /__ /_____

Stima indicativa della adesione ("*compliance*") del paziente alla terapia

☐ nulla ☐ scarsa ☐ soddisfacente ☐ ottima

C. FARMACI AL FOLLOW UP

Riportare TUTTI I FARMACI che il paziente sta assumendo al momento del follow up
(sia per i pazienti della coorte randomizzata che per quelli della coorte osservazionale)

DATA __ /__ /_____

Farmaco		*Dose (mg/die)*
Antipsicotici	*CLOZAPINA* ☐ SI' ☐ NO	
	ALOPERIDOLO ? ☐ SI' ☐ NO	
	ARIPIPRAZOLO ? ☐ SI' ☐ NO	
Antidepressivi		
Benzodiazepine		
Stabilizzanti dell'umore		
Anticolinergici		
Altri farmaci		

DA COMPILARE DA PARTE DI UN OPERATORE NON DIRETTAMENTE COINVOLTO NELLO STUDIO (se coorte randomizzata) oppure DALLO PSICHIATRA CURANTE (se coorte osservazionale)

BRIEF PSYCHIATRIC RATING SCALE (BPRS)

1 = Non presente **2 = Molto lieve** **3 = Lieve** **4 = Moderato** **5 = Moderatamente grave** **6 = Grave** **7 = Molto grave** **8 = Non valutato**

1. PREOCCUPAZIONI SOMATICHE	|___|	13. TRASCURATEZZA DELLA CURA DI SÉ	|___|
2. ANSIA	|___|	14. DISORIENTAMENTO	|___|
3. DEPRESSIONE	|___|	15. DISORGANIZZAZIONE CONCETTUALE	|___|
4. RISCHIO DI SUICIDIO	|___|	16. APPIATTIMENTO AFFETTIVO	|___|
5. SENTIMENTI DI COLPA	|___|	17. ISOLAMENTO EMOTIVO	|___|
6. OSTILITÀ	|___|	18. RALLENTAMENTO MOTORIO	|___|
7. ELEVAZIONE DEL TONO DELL'UMORE	|___|	19. TENSIONE MOTORIA	|___|
8. GRANDIOSITA'	|___|	20. MANCANZA DI COOPERAZIONE	|___|
9. SOSPETTOSITA'	|___|	21. ECCITAMENTO	|___|
10. ALLUCINAZIONI	|___|	22. DISTRAIBILITA'	|___|
11. CONTENUTO INSOLITO DEL PENSIERO	|___|	23. IPERATTIVITÀ MOTORIA	|___|
12. COMPORTAMENTO BIZZARRO	|___|	24. MANIERISMI E POSTURE	|___|

Note:

.....

.....

.....

.....

Per codificare la maggior parte degli item della BPRS si deve tener conto sia della frequenza sia della gravità dei sintomi. Può talvolta capitare che frequenza e gravità non corrispondano. In questi casi si suggerisce di utilizzare il principio gerarchico, cioè di assegnare il punteggio più elevato, sia che corrisponda alla frequenza, sia che corrisponda alla gravità.

Compilatore (nome e cognome) _____

DOMANDA: <u>solo per i pazienti della coorte randomizzata</u>

Secondo il compilatore, questo paziente, in aggiunta alla clozapina, sta assumendo:

ARIPIPRAZOLO I

ALOPERIDOLO

DA COMPILARE DA PARTE DEL PAZIENTE
(eventualmente con l'aiuto del medico o di un operatore)

Per favore, indichi se nell'ultimo mese ha lamentato i seguenti effetti collaterali, mettendo una crocetta dove ritiene appropriato

	Assente	Poco	Abbastanza	Molto	Moltissimo
52. Eritema	☐	☐	☐	☐	☐
53. Difficoltà a stare sveglio di giorno	☐	☐	☐		
54. Naso che cola	☐	☐	☐	☐	☐
55. Aumento dei sogni	☐	☐	☐		
56. Mal di testa	☐	☐	☐		
57. Bocca secca	☐	☐	☐		
58. Gonfiore al petto	☐	☐	☐	☐	☐
59. Geloni	☐	☐	☐		
60. Difficoltà a concentrarsi	☐	☐	☐		
61. Stitichezza	☐	☐	☐		
62. Perdita dei capelli	☐	☐	☐		
63. Urine più scure del solito	☐	☐	☐		
64. Irregolarità del ciclo	☐	☐	☐		
65. Tensione	☐	☐	☐		
66. Vertigini	☐	☐	☐		
67. Nausea	☐	☐	☐		
68. Aumento del desiderio sessuale	☐	☐	☐		
69. Stanchezza	☐	☐	☐		
70. Rigidità muscolare	☐	☐	☐		
71. Palpitazioni	☐	☐	☐		
72. Difficoltà a ricordare le cose	☐	☐	☐		
73. Perdita di peso	☐	☐	☐		
74. Mancanza di emozioni	☐	☐	☐		
75. Difficoltà a raggiungere l'orgasmo	☐	☐	☐		

(continua...)

(continua...)

	Assente	Poco	Abbastanza	Molto	Moltissimo
76. Fragilità delle unghie		☐			
77. Depressione		☐			
78. Aumento della sudorazione		☐			
79. Ulcere in bocca		☐			
80. Lentezza nei movimenti		☐			
81. Pelle grassa		☐			
82. Sonnolenza		☐			
83. Difficoltà ad urinare		☐			
84. Vampate al volto		☐			
85. Spasmi muscolari		☐			
86. Sensibilità al sole		☐			
87. Diarrea		☐			
88. Aumento della salivazione		☐			
89. Visione offuscata		☐			
90. Aumento di peso		☐			
91. Irrequietezza		☐			
92. Difficoltà ad addormentarsi		☐			
93. Dolore ai muscoli del collo		☐			
94. Tremori		☐			
95. Formicolii	☐	☐	☐	☐	☐
96. Dolori articolari		☐			
97. Diminuzione del desiderio sessuale		☐			
98. Macchie nuove o insolite sulla pelle		☐			
99. Movimenti involontari del corpo		☐			
100. Prurito		☐			
101. Mestruazioni meno frequenti	☐	☐	☐	☐	☐
102. Aumento della quantità di urina		☐			

Dopo aver compilato la "Scheda 3 – Follow up", procedere come segue:

SPEDIRE VIA FAX AL NUMERO 045 585871

- **Scheda 3 - Follow-up**

+

- **Scheda 2 - Variazioni di terapia**

dove sono stati riportati i cambiamenti di terapia avvenuti nell'arco di tempo intercorso dall'ultima valutazione effettuata per lo studio CHAT

OPPURE

Le schede compilate possono essere spedite anche tramite posta elettronica all'indirizzo:

studio.chat@medicina.univr.it

.....

In qualsiasi momento dello studio si dovessero verificare EFFETTI COLLATERALI

⇩

COMPILARE la SCHEDA 4 - "SEGNALAZIONE DI REAZIONE AVVERSA"

Appendice 4

Scheda di segnalazione di reazione avversa

SCHEDA 4 – SEGNALAZIONE DI REAZIONE AVVERSA

Numero identificativo CHAT: |___||___||___||___||___||___|

Iniziali del paziente (nome e cognome): |___||___||___|

Data di nascita: __ /__ /_____ **Sesso:** (M) (F)

C lozapine
H aloperidol
A ripiprazole
T rial

RIPORTARE QUALSIASI REAZIONE AVVERSA NEI PAZIENTI INSERITI NELLA COORTE RANDOMIZZATA O OSSERVAZIONALE

Il paziente rientra nella coorte |___| **1=randomizzata; 2=osservazionale**

Quale farmaco è verosimilmente responsabile della reazione avversa?

| Clozapina Aloperidolo Aripiprazolo | Altro .....

Dose (mg/die)	Data inizio trattamento	Data interruzione (SE SOSPESO)

Quale reazione avversa?

Tipo di reazione	Durata della reazione		Esito (in risoluzione, risolto, persiste)
	Data d'inizio	Data di fine	

Il paziente è stato ospedalizzato a causa della reazione? | **SI'** **NO**

Altri farmaci assunti negli ultimi 3 mesi?

Nome commerciale	Via di somministrazione	Dose (mg/die)	Assunzione del farmaco		Indicazione terapeutica
			Data inizio	Data fine	

Firma del medico ..... **data** .....

Nome in stampatello ..... **telefono** .....

Compilata la scheda, spedirla alla Segreteria dello studio CHAT (fax 045 585871)

Appendice 5

Scheda di variazione terapia

C lozapine
H aloperidol
A ripiprazole
T rial

Numero identificativo CHAT: |___||___||___||___||___|

Iniziali del paziente (nome e cognome): |___||___||___|

Data di nascita: __ /__ /_____ **Sesso:** (M) (F)

Nome del medico: ..... **Data della compilazione:** __ /__ /_____

Centro reclutante: .....

SCHEDA 2 – VARIAZIONI di TERAPIA

da COMPILARE da parte del medico DURANTE LO STUDIO

Riportare TUTTE le VARIAZIONI DI TERAPIA FARMACOLOGICA effettuate SUCCESSIVAMENTE all'ULTIMA VALUTAZIONE per lo studio CHAT

TERAPIA:			*VARIAZIONE:*			
Data	*Farmaco*	*mg/die*	*Aumento dosaggio*	*Diminu-zione*	*Aggiunta farmaco**	*Stop**
			=	=	=	=
			=	=	=	=
			=	=	=	=
			=	=	=	=
			=	=	=	=

** Coorte RANDOMIZZATA: (i) se si interrompe il trattamento con clozapina, aripiprazolo o aloperidolo OPPURE (ii) se si aggiunge stabilmente in terapia un farmaco antipsicotico COMPILARE SUBITO LA "SCHEDA 3 - FOLLOW-UP" e INVIARLA AL CENTRO OMS dell'Università di Verona (fax: 045 585871)*

Appendice 6

Lettera di approvazione dell'Agenzia Italiana del Farmaco

Agenzia Italiana del Farmaco

AIFA
DIREZIONE GENERALE

Roma, 30 gennaio 2007

Prot. AIFA/IC/I.9.a.b/10059

Prof. Michele Tansella
Principal Investigator - Studio CHAT
Sezione Psichiatria e Psicologia Clinica
Policlinico G.B. Rossi,
Piazzale L.A. Scuro 10
37134 VERONA

OGGETTO: Studio CHAT: Randomized evaluation of the effectiveness of clozapine and aripiprazole versus clozapine and haloperidol in the treatment of schizophrenia. An independent, pragmatic, multicentre, parallel-group, superiority trial.

Con la presente si comunica che l'Agenzia Italiana del Farmaco ha seguito il disegno e la stesura del protocollo relativo allo Studio denominato CHAT.

Si tratta di una valutazione dell'efficienza dell'utilizzo della clozapina e aripiprazolo verso clozapina e aloperidolo nel trattamento della schizofrenia. Trattandosi di uno studio di superiorità randomizzato indipendente, pragmatico, multicentrico sviluppato a gruppi paralleli, risulta di particolare interesse per la scrivente Agenzia.

Tale sperimentazione appare finalizzata al miglioramento della pratica clinica quale parte integrante dell'assistenza sanitaria.

Dott. Nello Martini
Il Direttore Generale
Nello Martini