INTRODUCTION

Psychopharmacologic treatment can suppress psychotic symptoms in most patients with schizophrenia. 10% to 30% of patients have little or no response to antipsychotic medications and up to an additional 30% of patients have only partial responses to treatment (1). The concept of nonresponse to treatment is multidimensional, as no response may be present in positive, negative, cognitive, or depressive symptom domains (2). Even if a patient’s positive symptoms respond or remit with an antipsychotic agent, residual negative and cognitive symptoms often persist (1).

There are several general principles for the treatment of refractory schizophrenia. When encountered by what appears to be treatment resistance, the clinician should review the diagnosis, check for psychiatric or substance abuse comorbidity, rule out medical comorbidities, and assess the adequacy of past and present pharmacotherapy (duration / dosage / compliance). Unfortunately, such data gathering is often made difficult due to poor history from the patient and a fragmented system leading to difficulty accessing medical records.

Treatment resistance may be related to suboptimal dosing of the antipsychotic, nonadherence with the prescribed medication regimen, ineffectiveness of the antipsychotic, or substance abuse (1).

Once treatment resistance is established, the clinician should identify areas of nonresponse; develop a sequential, systematic treatment plan; determine the length of each trial; define outcome criteria; and use a standardized rating scale to monitor response (eg, Brief Psychiatric Rating Scale, Positive and Negative Syndrome Scale). The clinician should consider that inadequate psychosocial treatment may create the appearance of treatment resistance (3).

Treatment-resistant schizophrenia can be defined based on little or no symptomatic response to multiple (at least 2) antipsychotic trials of an adequate duration (at least 6 weeks) and at therapeutic dose range (1). To open up thinking about treatment at this point in the illness, some psychiatrists have argued for replacing the term “treatment resistance” with “incomplete recovery” (2).

CLINICAL CASE REPORT

The patient IG, aged 48 years old, is hospitalized for visual complex figurative hallucinations and permanent complex commenting and imperative auditory hallucinations.
lucinations, hallucinating behavior, psychomotor restlessness, sleep disorder, major social and occupational dysfunction. From collateral relative antecedents it can be mentioned that patient’s brother is suffering from epilepsy.

The onset of the psychiatric disorder was at 34 years old, apparently unexpectedly, with visual zoopsial hallucinations and auditory hallucinations, symptomatology recovered with conventional antipsychotic (haloperidol) and anxiolytic-sedative treatment (diazepam). Since that time, the patient had yearly hospitalizations for psychotic recurrences with full interepisodic recovery.

From longitudinal symptomatologic course of the disease it results that the patient presented thought disorders: persecutory and reference delusions, external influence ideation (mental automatism Kandinski-Clerambault). Since 2001 perceptible productivity phenomenon had become permanent and hallucinating behavior had been installed. This psychopathological description caused clinically significant impairment in important areas of functioning, so that in 2002 the patient had retired from his activity.

The patient has a relationship with a person having a pathological condition from the same spectrum.

Along the course of the disease there have been given conventional and atypical antipsychotics: haloperidol, flupentixol, quetiapine, risperidone, aripiprazole, olanzapine, clozapine, duration of successful treatment being of several months.

**Mental Status examination:** The patient is dressed slatternly, with unsuitable hygiene, consciously, able to co-operate, hypomobile mimicry, paucity of expressive gestures. Unchanging facial expression. Lack of vocal inflections. Psychic contact easy to establish and maintain, poor visual contact; he is avoiding eye-to-eye contact, is looking downwards. Oriented to person, time and place. Reduced capacity to concentrate his attention. Social inattentiveness. Complex visual and auditory hallucinations with aggressive content. Impaired learning of new material and reduced ability to recall past experiences. Slowing down of ideational rhythm, ideative flood focused on automatisms of Kandinski-Clerambault. Impaired insight. Logical associations possible, ideative coherence still kept. Poverty of speech. Anxious mood. Affective flattening. Sleeplessness at awakening. Food appetite undisturbed. Hallucinating behavior. Psychomotor restlessness. Clinically significant social and occupational dysfunction.(He is able to do some useful activities). Relatively well preserved personality.

**Cerebral CT scanning:** Without supra- or infratentorial heterodense lesions visible at the native examination. Symmetrical ventricular system, with normal size. Slight thickening of the mucous membrane of jaw sinus, right ethmoidal cells and sphenoidal sinus.

**Positive diagnosis:** Paranoid schizophrenia

**Differential diagnosis:**
1. Other schizophrenia subtypes: undifferentiated schizophrenia, catatonic schizophrenia.
2. Psychotic Disorder due to a General Medical Condition;
3. Substance-Induced Psychotic Disorder;
4. Schizoaffective disorder;
5. Delusional Disorder;
6. Mood disorder with psychotic features;
7. Schizotypal Personality Disorder;
8. Schizoid Personality Disorder;
9. Paranoid Personality Disorder.

**Course and prognosis:**
- Natural course of the disease: ondulatory (exacerbations and remissions) towards deterioration.
- Factors of good prognosis: acute onset in adulthood, paranoid subtype of schizophrenia, good compliance with treatment.
- Factors of poor outcome: perceptual disturbances resistant to many pharmacologic treatment strategies; loss of work capacity, social abilities significantly impaired.

**Treatment:** consisted of pharmacologic and psychosocial approach. Long-term strategy should aim adequate antipsychotic treatment and the broadening of social support and care offered in difficult life situations. In our clinic, we have been given to the patient a combination of atypical neuroleptics: olanzapine 30mg/day and amisulpride 800mg/day with favourable evolution (reduced intensity of positive symptoms).

**Specific features of the case:** personality preservation to a certain extent, relatively well preserved cognitive processes, with incomplete affected emotional-volitional capacity.

**DISCUSSION**

Taking into consideration the specific features of the case presented we initially thought of reviewing the diagnosis. The possibility of having to do with a paraphrenia was based on Kraepelin’s definition from1909, once this nosological entity has been delimited from systematized delusions frame: «that endogenous psychosis characterized by a chronic systematized hallucinating delusion with fantastical nature, whose imagina
tive abundance, going almost to setting up a fantastical world, is contrasting with the long preservation of a behavior and an emotional life relatively corresponding to reality» (4).

A classification proposed by H.Ey and other authors settles thus the nosological position of chronic systematized delusions(4):
A. Without poor outcome:
- Chronic systematized delusional and hallucinating psychosis (paraphrenia).
- Other chronic hallucinating psychosis.
- Chronic delusional nonhallucinating psychosis (paranoia).

B. With dissociative course:
- Schizophrenia-paranoid subtypes.

It is possible that one subtype advances into another subtype, but also to be fixed in a certain type. Within the framework of chronic delusional disorders we can speak about species of the same kind, not about different kinds. Looking at the unity of delusional disorders of personality in dynamic perspective, some authors concluded that the pathological process is unfolding in different stages. Thus they have differentiated paranoic, paraphrenic and schizophrenic stages (4).

Durations for therapeutic success of anterior antipsychotic treatments are in concordance with the latest data literature.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), initiated by the National Institute of Mental Health in U.S.A., is a study involving comparison of four second generation antipsychotics (olanzapine, quetiapine, risperidone and ziprasidone) and one first generation antipsychotic (perphenazine) for the treatment of schizophrenia under double-blind randomized conditions (Lieberman et al., 2005). The primary outcome of the study was to assess the effectiveness of the different treatments. Effectiveness was conceptualized as a combination of efficacy and tolerability. The study duration was planned for 18 months in the first phase with a double-blind condition of treatment. After discontinuation from the first phase, patients could be assigned for other treatments in phases 2 and 3. An analysis of the «duration of successful treatment» is among many considerable results of the study. The comparisons using this parameter revealed significant differences between olanzapine vs quetiapine (p=0.001), riperidone (p=0.002) and perphenazine (p=0.013), and for risperidone vs. quetiapine (p=0.021). In absolute number, the duration of successful treatment was 3 months (2-5 months) for olanzapine; in all other groups, the duration of successful treatment ranges 0-1 or 0-2 months (5).

Clozapine remains the ‘gold standard’ of treatment for schizophrenic patients with treatment-resistant symptoms. However, a considerable number of patients treated with clozapine are still nonresponsive or only partially responsive. The combined application of antipsychotic drugs is an established step in the cascade of treatment strategies of treatment-resistant schizophrenics (6, 7). Use of antipsychotic polypharmacy is still controversial, but occurs frequently within clinical practice, with rates ranging from 5% to 18% in outpatients and up to 50% or even more in inpatients (8, 9). These polypharmacy usage patterns are in contrast with most published treatment guidelines (10, 11) and should be limited to severe cases and only if monotherapy with different classes of first- or second-generation antipsychotics in sufficient doses over an adequate time period have proven ineffective.

It is increasingly acknowledged that the time taken to respond to clozapine for some individuals may be up to or beyond 1 year. In particular, time to response may be longer for patients with past episodes, as each successive episode may increase the time to remission. In light of these findings, combination therapies involving clozapine should be considered only if the treatment duration with clozapine monotherapy was 6–12 months.

There are four double-blind, placebo-controlled studies of combinations of clozapine and other antipsychotic drugs in the literature (12), but most investigations have been conducted with an open uncontrolled design and have included only a small series of patients. Risperidone is the most extensively documented clozapine augmentation agent. A double-blind study (12) and two uncontrolled prospective studies (13) reported improvement with the combination, with no significant increase in adverse effects. In contrast, a double-blind study and an uncontrolled prospective trial reported no benefit.

The combination of sulpiride or amisulpride, which are relatively selective D2 antagonists, and clozapine has shown promising effects in different studies (14, 15). In all of these studies, the investigators reported a significant benefit in terms of improvement of psychopathological state and adverse effects. Furthermore, daily clozapine doses could be reduced and lower individual drug doses could be used in combination therapy compared with monotherapy.

Other investigators have reported on the combination of ziprasidone and clozapine, amisulpride and olanzapine, risperidone and amisulpride, and ziprasidone and amisulpride (16, 17).

A clinical observation conducted by Ziegenbein M, Wittmann G and Kropp S, in 2005, tested the efficacy of the combination between aripiprazole 15-35mg/day and clozapine 400-850mg/day at eleven patients with treatment-resistant schizophrenia. Patients had to have remained on a stable dose of clozapine for at least 6 months in order to ensure a reasonable opportunity to respond to clozapine monotherapy. Clinical status was evaluated at baseline and at 3 months’ follow-up using the Brief Psychiatric Rating Scale (BPRS). Treatment response was defined as a reduction in total BPRS score of ≥20%.

All patients completed 3 months’ combination treatment. There was a significant reduction in the mean BPRS score in seven patients (63.6%) over the 3 months of combination treatment. Augmentation with aripiprazole in clozapine-treated patients did not result in a corresponding increase in adverse effects. Use of the combination allowed a significant reduction in the daily dose of clozapine. Combined application of cloza-
pine and aripiprazole is in accordance with a neurobiological rationale, because aripiprazole has greater affinity for D2 receptors compared with clozapine.

The mechanisms underlying the combined action of antipsychotics still remain unclear. Most authors have suggested that the additive pharmacokinetic effect on dopamine D2/D3 receptors might be the most important synergistic mechanism to explain the favourable therapeutic outcome of combination strategies (18). Some authors believe that the efficacy of the combination of atypical antipsychotics and clozapine may be attributable to the synergistic receptor profiles of the two substances, rather than to a pharmacokinetic phenomenon.

The stability of serum clozapine levels over the investigation period in some studies suggests that the benefit of the combination strategies of atypical antipsychotics to clozapine is not a consequence of increasing serum clozapine levels, which would constitute a pharmacokinetic interaction.

Positron emission tomography (PET) data demonstrate that D2 receptor occupancy of 70% is necessary for therapeutic benefits, while occupancy of >80% is associated with extrapyramidal symptoms (19).

The risks of antipsychotic polypharmacy have not been well studied, and information about long-term risks is particularly sparse.

In terms of augmentation with mood stabilizers, there have been described only 2 double-blind studies. The first study used lithium, and aimed for a therapeutic lithium level of 0.5 mEq/L. Patients with schizophrenia, with a decrease of > 20% on the BPRS total score (22).

Sarcosine (glycine transporter inhibitor) is more efficient than NMDA agonists (D-serine, glycine, D-cycloserine) in acute phase of schizophrenia (23).

Although pharmacologic treatment is a necessary first step in managing incompletely recovered patients, adjunctive psychosocial interventions are often needed to optimize treatment success. Cognitive-behavioral techniques for schizophrenia have developed over the past few years against a backdrop of skepticism. Yet evidence to support the use of CBT is substantial enough so that many guidelines are recommending it for every patient with schizophrenia, especially those with treatment resistance (24). Most research on CBT in schizophrenia has been conducted using approximately 20 sessions, with each session lasting up to an hour (though sessions can be shorter). To date, more than 20 randomized controlled trials of CBT in schizophrenia have been conducted, indicating a beneficial effect on positive, negative, and depressive symptoms.

In CBT, the focus on understanding symptoms helps patients accept and continue medications. Insight is approached systematically, and engagement with the patient is strongly emphasized. There is often a focus on understanding the first episode when positive symptoms initially appeared, so that the patient has to make sense of these experiences. To handle delusions, the therapist gathers information on current beliefs and the links between thoughts, feelings, and behavior. Possible alternatives to the delusional beliefs are explored, investigating and reality testing are encouraged, and the inference chain is gently examined. In addition, the nature of hallucinations is clarified, and the patient is assisted with appropriate attributions, examining the content of hallucinations and exploring coping strategies. Negative symptoms are also targeted, and a focus is on learning to cope with stimulation rather than withdrawing from it. Of course, CBT is not effective for every patient, especially those who are very psychotic, but this treatment strategy can be complementary to pharmacotherapy for many patients.

**CONCLUSION**

Current treatment strategies in treatment-resistant schizophrenia include:
- switching antipsychotic agents;
- a trial of a high-dose atypical antipsychotic;
- initiation of a trial of clozapine;
- augmentation of clozapine or another atypical antipsychotic agent;
- cognitive-behavioral therapy.

**REFERENCES**


24. West J. Trends and characteristics of inpatient treatment in routine psychiatric practice in the U.S.. Program and abstracts of the American Psychiatric Association 2005 Annual Meeting; May 21-26, 2005; Atlanta, Georgia. Symposium No48B.