IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 23, Issue 2 Ser. 8 (February. 2024), PP 15-21
www.iosrjournals.org

Reflection On A Clinical Case Of Resistant Schizophrenia

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Abstract:
Resistant schizophrenia is defined as an inadequate response to two different antipsychotic treatments of sufficient duration and dosage. Clozapine is the only drug treatment currently approved for patients with resistant schizophrenia, and is associated with a lower rate of relapse and hospitalization than other antipsychotics. However, around 30% of patients will not respond to it, and will present residual symptoms causing a notable impact on quality of life, socio-professional integration and increasing psychiatric comorbidities, which represents a real public health problem, in terms of cost and management. While several arguments suggest that clozapine is effective for patients suffering from resistant schizophrenia, the delay in initiating it represents a real factor limiting its efficacy. Consequently, prescribing clozapine as soon as possible will maximize its benefits. However, long delays in initiation have been reported in current clinical practice. However, other non-pharmacological therapeutic alternatives can be proposed for the treatment of positive symptoms of clozapine-resistant schizophrenia, notably electro-convulsive therapy (ECT). This article presents a case study illustrating the psychiatric course of a young patient suffering from resistant schizophrenia. Through a review of the literature, we attempt to better define the contours of this clinical entity, which lacks a consensual definition, and we discover the reference treatments for resistant schizophrenia, and finally the associative possibilities of different treatments depending on the patient's symptomatology.

Keyword*: Schizophrenia, Therapeutic resistance, Clozapine, Electroconvulsive therapy*

Date of Submission: 19-02-2024 Date of Acceptance: 29-02-2024

I. Introduction

Schizophrenia is a serious, chronic mental illness affecting young people (1% of the general population) [1]. It associates a triad of positive, negative and cognitive symptoms according to the dsm-5 [2]. Its course and prognosis are variable. 30% of patients do not respond to antipsychotic treatment, and schizophrenia is said to be resistant[3]. Resistance is defined as the persistence of symptoms despite two lines of antipsychotic treatment from at least two different drug classes at effective doses for minimum durations of more than six weeks [4]. Clozapine is currently recommended as the treatment of choice for resistant schizophrenia, with good efficacy [5]. However, around 30% of patients will fail to respond [6], with residual symptoms having a significant impact on quality of life and increasing psychiatric comorbidities (anxiety, distress and addiction), representing a real public health problem in terms of cost and management. Lack of response also means long periods of hospitalization, complicating these patients' social, educational and professional reintegration.

Numerous pharmacological therapeutic combinations in addition to the usual antipsychotic background treatment have been tried, without conclusive results or validated benefit in favor of a specific combination. However, other non-pharmacological therapeutic alternatives may be proposed for the treatment of positive symptoms of clozapine-resistant schizophrenia, notably electro-convulsive therapy (ECT)[7]. According to a review by Lally et al,[8] increases the overall response to clozapine by 76% [8]. Indeed, the American Psychiatric Society recommends ECT as a treatment of choice in cases of therapeutic ineffectiveness or in patients who have responded well to this therapy in previous episodes of illness, or as a second choice in cases of resistance to drug treatments [9]. However, despite efficacy on positive symptoms, notably auditory hallucinations, results remain equivocal across studies, with considerable intra-individual variability [9-10].

This article presents a case study illustrating the psychiatric course of a young patient suffering from resistant schizophrenia. Through a review of the literature, we attemp to better define the contours of this clinical entity, which does not have a consensual definition, and we will discover the reference treatments for resistant schizophrenia, and finally the associative possibilities of different treatments according to our patient's symptomatology.

II. Patient and observation

I'm naming this patient Nabil, a young man, aged 25, single, a student in his 2ème year as a pharmacist, who is taking a break from his studies.

Biographical information :

Nabil's mental problems date back to the age of 18 (late teens), a year after his parents divorced. He is the eldest of three boys. He passed his Baccalaureate with honors very well. He started out at a top computer science school, but a year later changed his course of study and enrolled in the Faculty of Pharmacy. This coincided with the onset of disorders that interfered with his studies, resulting in poor academic performance and an inability to keep up with his studies, which were an additional source of stress for his illness. He was placed on academic leave by his attending physician until stabilization, but alas, Nabil was never able to resume his studies due to the worsening of his mental condition.

Psychiatric care:

His first acute psychotic episode occurred at the age of 18, after he had passed his Baccalaureate exam, and rapidly resolved after four months of outpatient antipsychotic treatment. He was hospitalized for a second psychotic episode after discontinuing treatment a year later, marked by severe behavioral disturbances and bizarre behavior. There was a great deal of anxious perplexity, even to the point of fragmentation anxiety. Sudden mood swings and polymorphous delusional activity with themes of poisoning, bewitchment and denial of filiation, essentially intuitive and hallucinatory in mechanism. The diagnosis of schizophrenia in its productive form was retained according to the dsm-5 (Tab.1).

Table 1 : diagnostic criteria for schizophrenia according to dsm-5 [2]

Schizophrenia Diagnostic Criteria 295.90 (F20.9)
A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3): **1.** Delusions. **2.** Hallucinations. **3.** Disorganized speech (eg, frequent derailment or incoherence). **4.** Grossly disorganized or catatonic behavior. **5.** Negative symptoms (ie, diminished emotional expression or avolition). B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset. C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (ie, active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form. D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either **a)** no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or **b)** if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness. E. The disturbance is not attributable to the physiological effects of a substance or another medical condition. F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated) .

The anxiety was rapidly relieved by second-generation antipsychotics and anxiolytics, with partial regression of the disorders. Despite good compliance with antipsychotic treatment at suitable doses and durations, the clinical picture worsened over the months and years, with the onset of pathological reticence, mimic parasitism, gestural stereotypies and hallucinatory equivalents, i.e. listening attitudes, soliloquies and side-talk with numerous immotivated laughs. The young patient is unable to concentrate, very detached from the environment and confined to his autistic world. Numerous prescriptions of new-generation antipsychotics and attempts at therapeutic combinations have been made, but to no avail. Faced with the scarcity of clozapine, Nabil benefited from second-generation long-acting antipsychotics, Paliperidone Palmitate "Xéplion®" at 150mg every four weeks, then in combination with risperidone gout, given the lack of response.

More than four years after the evolution of the disorders and a therapeutic resistance, for the first time, the young patient benefited from clozapine 100mg tablets, 6 tablets divided into three doses, after incremental increase and regular monitoring of his blood count and cardiac condition. Unfortunately, no response was noted after eight weeks of treatment. The decision was made to combine aripiprazole with two 15 mg tablets daily. After a week, we were forced to stop the clozapine in view of the disturbance in the blood count (onset of agranulocytosis) and the appearance of neurological side effects, namely severe extrapyramidal syndrome.

III. Psychiatric examination

The clinical case includes elements of discordance (mimicry parasitized by stereotyped movements, detachment from the atmosphere). Delusional ideas remain very present in the speech. Pathologically, there is considerable ambivalence and ideo-affective discordance with regard to affects. At times, accelerated verbal flow

and affective detachment, apathy and the presence of paradoxical feelings with paramimia, including immotivated smiles and laughter. Psychic and auditory hallucinations invade the mind, leading to the adoption of listening attitudes. Nabil is distrustful and suspicious, and denies all disorders (poor insight).

Behaviorally, he exhibits incessant shoulder and upper limb movements, as well as extremity tremors, indicative of extrapyramidal neurological side-effects. The patient takes cannabis in search of sedation of neurological effects and correction of insomnia. In addition, the patient manifests akathisia, resulting in difficulty in holding the same position, leading to psychomotor instability. In terms of negative symptoms, apragmatism and autistic withdrawal, as well as social withdrawal with detachment from the external environment, were reported by the mother and observed during his hospitalization.

– Assessment of symptom severity using the PANSS (*Positive and Negative Syndrome Scale)*: total score= 80
Positive symptom subscore = 32
Negative symptom subscore = 18
A sub-score of psychopathological symptoms = 30
The damage is considered severe.
– The Global Assessment of Functioning (GAF) =29 scale indicates dysfunction in all areas. Behaviour is significantly influenced by delusions and hallucinations.

IV. Discussion

Young Nabil, 25 years old today, single, with a university education (2ème year Medicine) and three years off school, is being treated for a **productive form of schizophrenia that is resistant to** therapy, despite good compliance with treatment. The eldest of three boys, he grew up in a family environment marked by marital conflict, leading to a parental divorce at the age of 17. Nonetheless, he passed his baccalaureate exam with flying colors, and went on to study at university.

The onset of the disorder dates back to late adolescence, with an acute psychotic decompensation. A second decompensation a year later marked the onset of the schizophrenic process, characterized by severe behavioral disorganization, delusional, and hallucinatory activity resistant to first- and second-generation antipsychotic treatments. Various hospital stays, practically one a year, with long stays of 3 to 4 months.

Cannabis consomption

Cannabis has been used in times of distress (invasion by psychotic anguish), without any notion of therapeutic discontinuation for anxiolytic purposes, and is a major factor in comorbidity. Some studies tend to show that substance abuse diminishes the efficacy of antipsychotic treatment: in 262 schizophrenics, there was a significant difference in the response rate to treatment (olanzapine or haloperidol) at twelve weeks between the "substance abuser" group (27%) *and the* "non-drug abuser" group (35%) [11].

In a group of 49 schizophrenic patients taking their medication correctly, rehospitalization took place at an average of ten months in the "substance abuser" group, *versus* 37 months in the "non-drug abuser" group [12]. According to E. J. Khantzian, *"The drugs used are not chosen at random. The choice of product is the result of an interaction between its psychopharmacological action and the dominant feeling that is most distressing for the patient."* [13]

Cannabis use has been described as having a facilitating effect on dopaminergic neurotransmission in the mesocortical system. In the hypothesis of self-medication, this product would have the function of relieving the negative symptoms and cognitive difficulties of the schizophrenic patient [14].

We also raised the issue of an attempt to prescribe several antipsychotics with different combination regimens, including a long-acting atypical antipsychotic: Paliperidone Palmitate "Xéplion®" in high dose and in combination with aripiprazole. There is a delay in starting clozapine five years after the onset of symptoms.

Therapeutic resistance :

Recently, international guidelines on therapeutic resistance have included in their definitions the mandatory failure of at least two trials of different antipsychotics, at sufficient dose, before speaking of resistance. The minimum duration of these therapeutic trials varies between 2 and 8 weeks. These guidelines specify that at least one of the antipsychotics tested must be of the second generation [4].

Here is a summary of the definitions of the different recommendations in Table 1, according to the American Psychiatric Association (APA), The Texas Medication Algorithm Project (TMAP), the Haute Autorité de Santé (HAS), the Schizophrenia Patient Outcomes Research Team (PORT) and the World Federation of Biological of Societies Psychiatry (WFSBP) (Tab.1) [15-19].

Table 1: Summary of the various recommendations defining resistant schizophrenia

Recommendations by year	Number of antipsychotics to try	Treatment duration	Atypical antipsychotics?
APA (2004) [15]	2	6 weeks	Not recommended
TMAP (2007) [16]	**2**	**Not defined**	**Yes, on the front line**
HAS (2007)[17]	2	Not defined	Yes
PORT (2010) [18]	2	8 weeks	Not recommended
WFSBP (2012) [19]	2	2 to 8 weeks	Yes

- With regard to the various protocols for prescribing antipsychotics prior to starting clozapine, maximum doses were reached, but were reduced in view of tolerance problems.
- Over the past year, we have seen a direct link between episodes of symptom exacerbation and increased cannabis use.
- Current psychiatric examination shows very limited awareness of disorders = lack of insight.

Lack of insight, substance abuse and failure to adhere to therapy at the onset of the disorder are factors in poor response to antipsychotic treatment. The existence of these factors in our patient seems to support the notion of therapeutic resistance.

Faced with these therapeutic failures and psycho-education, the only therapeutic strategy left as an option for our patient was to combine pharmacological treatments with electro-convulsive therapy ("seismotherapy") sessions to consolidate therapeutic effects. All in all, given the patient's good compliance with treatment this past year, his young age and the ambition to resume his studies, we ultimately preferred a combination of olanzapine, whose molecular structure is similar to that of clozapine, with ECT sessions, to give him a better chance of achieving remission of his illness.

ECT sessions were scheduled twice a week, with supervision of a resuscitator and mild general anesthesia. At the end of the 6th session, Nabil began to have an early remission of his psychotic symptoms. There was a significant reduction in the severity of positive and, above all, negative clinical symptoms, with PANSS sub-scores as follows:

Positive symptom subscore = 16
Negative symptom subscore = 16
A sub-score of psychopathological symptoms= 28
Total score= 60

This therapeutic combination appeared to be effective in our patient. We decided to maintain a few sessions of ECT to consolidate the therapeutic effects of the antipsychotic at the rate of one session every two weeks. From this clinical case, we can say that the therapeutic response is individual and personalized. In other words, there are individual variations of a genetic, biological, and probably clinical nature.

Clozapine

Clozapine is an "atypical" antipsychotic molecule of the dibenzodiazepine class, developed in the early 60 s by Swiss pharmaceutical companies [20]. Clozapine is currently considered the treatment of choice for resistant schizophrenia [21], being more effective than both typical and atypical neuroleptics. It is more active not only on positive symptoms, but also on the negative and cognitive symptoms of the disease, and reduces the risk of suicide in the schizophrenic population [22]. It is the drug with the fewest extrapyramidal side effects. It is, however, highly toxic to the body. Being metabolized by neutrophils, it causes agranulocytosis in 3.8 to 8 ‰ of cases, lethal in 0.1 to 0.3 ‰ of cases [23]. However, a strict pre-therapeutic workup and regular monitoring of the molecule's blood levels allow it to be used.

Despite current definitions of resistant schizophrenia and clinical recommendations, clozapine still has only a modest impact in current practice. Indeed, clozapine is a first-line treatment for resistant schizophrenia, not a last-chance treatment, as in the case of our patient and many others. Although several arguments suggest that clozapine is effective for patients suffering from resistant schizophrenia, the delay in its introduction represents a real factor limiting its efficacy [24]. Consequently, prescribing clozapine as soon as possible will maximize its benefits. Howes and al. 2012 and other authors demonstrate that it is introduced with a delay of 4 years, in many patients treated with several high-dose drugs, which runs counter to current good practice recommendations [25], which is in line with our patient's case. However, even if practitioners propose this molecule at the outset of treatment, patients often refuse. Consequently, the delay in initiation is partly linked to a lack of patient consent, which does not always reflect the care offered by physicians. Other authors point out that delays in initiation penalize patients, and result in lost opportunities. They add that they often receive several lines of treatment beforehand.

The problem is that the longer the treatment is ignored, the more reluctant patients become to prescribe it. The risks associated with drug side-effects are also raised. Indeed, iatrogenicity is another factor in poor

adherence to treatment, and can therefore generate therapeutic resistance. The most poorly tolerated side effects are neurological (akathisia, akinesia, muscular rigidity, anticholinergic signs), metabolic, sexual and haematological, as in the case of our patient [26] (Tab.2).

Table. 2: The main non-extrapyramidal effects of drugs indicated for psychosis and anxiety.in particular clozapine, are listed in the following table [26]:

Undesirable effects	Comments
Sedation	Chlorpromazine and clozapine are highly sedating at the start of treatment, which justifies readjustment of treatment and the choice of an appropriate molecule if necessary.
Convulsions	**They are rare, unless there is a predisposition; risperidone does not alter the epileptogenic threshold, but clozapine facilitates the onset of seizures.**
Orthostatic hypotension	Many molecules seem to give rise to this effect at the start of treatment, and a gradual increase in dosage is necessary, especially in the elderly.
Cardiotoxicity	Clozapine should be avoided in patients with a history of cardiac disease. Arrhythmias are common in clozapine overdose (see Interactions table).
Anticholinergic effects	Clozapine and olanzapine are powerful anticholinergics; risperidone has no effect. Measures to limit anticholinergic effects are of limited effectiveness. In the event of abrupt discontinuation of an anticholinergic neuroleptic, care should be taken to avoid a "cholinergic rebound" with nausea, vomiting, anorexia, hypersudation, diarrhea, agitation, anxiety and insomnia.
Weight gain	All antipsychotics carry a risk of weight gain, but the incidence and significance of this iatrogenic effect vary (low, for example, with aripiprazole or risperidone). The only answer remains prevention through physical activity and dietary advice.
Sexual disorders	Numerous and poorly assessed due to the patient's reluctance to mention them, they are thought to result in particular from the anticholinergic effects of various antipsychotics.
Hematological effects	Transient leukopenia is common with phenothiazines. **Severe agranulocytosis** has been reported with clozapine, requiring regular haematological monitoring.
Hormonal effects	It is important to monitor blood sugar levels in patients on antipsychotic drugs (continuous monitoring for six months at the start of treatment, and every three months thereafter in at-risk patients). Basic dietary measures must be rigorously applied and taught on an ongoing basis. Blockade of pituitary D2 lactotroph receptors induces an increase in prolactin levels. The phenomenon is transient with clozapine and discreet with the most recent molecules. Dysmenorrhea is frequent with benzamides, and is sometimes treated with bromocriptine.

Psychoeducation

Psychoeducation and the combination of other molecules may be necessary adjuncts in the event of an inadequate response. Indeed, Hogarty and colleagues [27] have shown that psychoeducation has become essential to therapeutic efficacy, particularly in schizophrenia. Psychoeducation is not simply reduced to its pedagogical dimension, but is seen as a genuine therapy, as it aims, in fine, to modify behaviours and thoughts. In 2011, Petit Jean's article on the effects of psychoeducation [28] underlines the benefits of psychoeducation on multiple clinical dimensions, both for the patient and those close to him or her.

Electroconvulsive therapy (ECT)

ECT can be used for patients resistant to clozapine, or for those for whom this molecule is contraindicated, even after therapeutic results have been obtained, which is in line with our decision concerning our patient. ECT has been used to treat schizophrenia since the 1940s. It consists of inducing brief epileptic seizures via brain stimulation with a variable-frequency electrical current using electrodes placed on the scalp, performed under general anaesthetic. Biochemically, ECT acts on the dopaminergic system, increasing the number of D1 and D2 dopamine receptors and dopamine release from the brainstem, modulating the serotonergic system to modulate dopaminergic effects, and increasing the number of GABA receptors in the occipital cortex. It also induces an increase in BDNF, which is involved in neurogenesis [8].

Several research studies [29] have attempted to demonstrate the efficacy of combined ECT and antipsychotic therapy in resistant schizophrenic patients, as well as the clinical factors predictive of a good response [29]. The results were in favour of a significant reduction in the severity of clinical symptoms, with negative signs predominating, improved treatment responses with greater effects on positive signs, and a shortening of the duration of the current episode. Another study corroborates the above findings [30], investigating the effects of long-term combination ECT with three different antipsychotics (Haloperidol, Amisulpride, Olanzapine) in the treatment of resistant schizophrenia, concluding that this long-term combination is more effective [30]. ECT can be proposed as [29-30] :

- As a curative treatment, the main indications are catatonic schizophrenia and acute delirious exacerbations, especially in cases of significant productive symptoms, such as accoustico-verbal hallucinations that generate severe anxiety and are responsible for the risk of auto or hetero-aggressive acting out, which is the case with our patient.
- In combination with clozapine or other atypical neuroleptics, significantly improves symptoms.

− Maintenance treatment, which consolidates the therapeutic effects obtained with curative ECT.

Shimizu et all [31] describe a case of disorganized schizophrenia resistant to pharmacological treatments for 7 years, who responded remarkably well to ECT during the curative phase of treatment. It should be noted that, in addition to consolidating therapeutic benefits, maintenance ECT leads to a reduction in the dosage of antipsychotic drugs, which would be useful for increasing tolerance and hence adherence to treatment. Carrying out ECT at one, or even two, sessions a month would encourage therapeutic support for patients receiving clozapine, enabling blood counts to be monitored during pre-anesthesia check-ups.

While ECT treatment has proved effective in the majority of psychiatric pathologies, this remedy is not without its side effects, which can be classified into three types [10]:

− Cardiovascular effects, as the induced generalized convulsive seizure represents the equivalent of a stress test;
− Somatic effects such as headaches, muscular pain, epilepsy, and more,
− Cognitive effects. These are assessed by neuropsychological tests, which show the frequency of memory disorders.

In view of this succinct survey of clozapine-resistant schizophrenia and management modalities, the combination of ECT with clozapine appears to be the best therapeutic option for treating the positive symptoms of clozapine-resistant and refractory schizophrenia in our patient under strict supervision. There are no clear clinical recommendations as to the indication of other therapeutic alternatives, notably transcranial magnetic stimulation (rTMS), or cognitive-behavioral therapy or meta-cognitive therapy [32]. Their efficacy, however, is heterogeneous and equivocal, and the results of studies remain preliminary [32-33]. At present, no criteria have been validated, but their definition and research will enable optimal, individualized therapeutic choices in the future. Furthermore, the inter-individual variability of response to treatment prompts the identification of phenotypic, neurobiological and clinical eligibility criteria in order to predict response to treatment and define subgroups of responders or non-responders, for example to rTMS [33].

V. Conclusion

Despite the growing number of antipsychotic molecules available, psychiatrists are still faced with the problem of some of their treatments failing. Numerous alternatives exist for the treatment of positive and negative symptoms of schizophrenia resistant to most first- or second-generation antipsychotics, notably clozapine. Clozapine is only used in cases of resistance to first-line treatments, notably atypical neuroleptics. However, over 50% of patients remain symptomatic even on clozapine, and cases o f ultra-resistance have even been reported. Nevertheless, a number of therapeutic combinations can be used, including electroconvulsive therapy, transcranial magnetic stimulation (rTMS), transcranial direct current magnetic stimulation (tDCs), cognitive-behavioural therapy and cognitive-behavioural meta-therapy in combination with the antipsychotic. Their efficacy, however, is heterogeneous and equivocal, and the results of studies remain preliminary. Nonetheless, they remain interesting therapeutic perspectives.

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