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Combined pharmacological and psychosocial interventions in resistant schizophrenic patients: what should be the main outcome? Clinical suggestions from a literature review

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Summary

Background. Treatment response in schizophrenia patients is a multidimensional concept. Remission in schizophrenic patien has been defined as the reduction of symptoms with mild disability, while recovery refers to regaining functioning and social skills. The main goal of schizophrenia treatment seems to be symptomatic remission and this could be the reason why great emphasis is focused on drug treatments. Little is still known about psychosocial interventions in drug-resistant schizophrenic patients. We may wonder about the effectiveness of psychosocial intervention in resistant schizophrenia and the possibility of functional recovery in drug-resistant patients showing just partial clinical remission.

Methods. We report a case of early onset schizophrenia in a young female patient strongly refractory to third-line therapy with clozapine. All data were collected and recorded during the patient engagement in Mental Health Day Service, where Cognitive Remediation Training and family interventions were performed.

Results. After nine months of continuative psychosocial interventions combined to psychopharmacological treatments,our patient performed HoNOSRome, BPRS SAPS and SANS, and satisfied Criteria for Functional Recovery from Schizophrenia, although positive symptoms persistence.

Conclusions. Even when a complete remission is not observed, difficult to treat patients could achieve functional and social outcomes thanks to psychosocial interventions combined with a pharmacological approach that should be more tolerable for them, although less effective against symptoms. It is possible that a good functional recovery,even supposing a partial or in complete remission, could bestow to these patients a good quality of life, that should be the aim of every psychiatric and medical intervention.

Key words: clozapine, aripiprazole, add-on therapy, psychosocial intervention, schizophrenia, psychosis, difficult-to-treat patients, recovery, functional recovery

Introduction

Treatment response in schizophrenia patients should be a multidimensional concept, including clinical and psychosocial outcomes, work ability and cognitive performance [1,2]. Recovery, referring to patients regaining functioning and participating in social and vocational opportunities, is the ultimate goal of

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treatment in schizophrenia [3]. Remission is a necessary but not sufficient step toward recovery [4]: it has been defined not as the complete absence of symptoms but rather as the reduction of symptoms with mild disability [5]. As it is known, antipsychotic monotherapy is the first line treatment for schizophrenia [6], but in clinical practice schizophrenic patients' management is usually based on strategies combining pharmacotherapy and psychosocial interventions, a mixture of medical, social (community and family based intervention), and psychological (especially Cognitive-Behaviour Therapy) interventions aimed at the social integration of the patients [7]. Despite combining strategies, many schizophrenic patients are difficult to treat: they could show drug resistance or inadequate response to psychosocial therapies, they could be non- compliant, aggressive and violent [1]. Around 30% of patients are considered refractory to first-line drug therapy due to uncomplete clinical control of positive and negative symptoms [8]. In these patients at least two trials with different second generation antipsychotic drugs have to be attempted before starting to administer clozapine that remains the most effective drug [9] and the only evidence-based medication for treatment-resistant schizophrenia [6]. Notwithstanding there are few studies about psychosocial interventions in resistant schizophrenia, NICE guidelines had recently added recommendation for psychotherapies and family interventions in association with clozapine [6]. We report a case of early onset schizophrenia in a young female patient with a history of several psychopharmacological trials who has been engaged in our Mental Health Day Service. Although a complete remission had not been observed in this patient, improving in both social and instrumental activities of daily life was obtained. We may wonder about the effectiveness of psychosocial intervention in resistant schizophrenia and the possibility of functional recovery in drug- resistant patients even though the clinical remission is partial.

Materials and methods

We report a case of early onset schizophrenia in a young female patient strongly refractory to therapy. All data were collected and recorded during the patient engagement in Mental Health Day Service. BPRS, SAPS and SANS, and HONoS Rome assessment were performed at baseline and after nine months. Plasma levels of clozapine were tested after one year of continuative drug therapy.

Results

A.A., female, 24 years old, university student, with a history of stressful events, came to the attention of our Mental Health Department after several years of medical care at other centers. The psychotic onset occurred at age 17 with ideas of reference, persecutory delusions, auditory hallucinations of sexual content. Positive symptoms improved after treatment with Risperidone 1 mg/day but she became physically and verbally aggressive. After therapy-interruption aggression persisted and academic performance got worse. Afterwards her illness did not respond to or she did not tolerate haloperidol, bromperidol and olanzapine. In December 2014 her disease got worse and she was hospitalized for insomnia, auditory hallucinations, fatuous affect, disorganized symptoms, sinus tachycardia. After a wash out period, a therapy with Clozapine (250 mg/day) was started with little improvement of symptoms. Severe sedation and psychomotor retardation were observed as side effects. The patient came to our center at the beginning of 2015. In an attempt to manage side effects, Clozapine dosage was reduced to 175 mg/day while Aripiprazole was increased to 30 mg/day [10]. Sodium Valproate granulation (500 mg/day) was added to have a greater improvement in symptoms [11]. Sedation and psychomotor retardation improved and there was no worsening of positive or negative symptoms. During this period a Psychodynamic Psychotherapy was started. Despite some initial difficulties since September 2015 she became compliant and sessions were performed once per week. In February 2015 A. engaged in our Mental health day services participating in unstructured activities which included cognitive interviews. In June 2015 The Health of the Nation Outcome Scale HoNOS [12] translated and adapted into Italian: HoNOS Rome [13] was applied to assess the social functioning of our patient and the caregivers distress. HoNOS scale includes also The FACE core assessment used for the routine measurement of disability and clinical outcomes. In August 2016 she started to participate in structured activities including Cognitive Remediation Training [14] and family interventions [15] with a little improvement in symptoms and in her social activities. In February 2016 due to the persistence of auditory hallucinations we decided to monitor blood levels of clozapine [16]. The clozapine plasma concentration was 170 ng/ml, while according to our lab the therapeutic range for treatment of schizophrenia is 100-700 ng/ml.

HoNOS Rome and FACE core were reassessed showing a better performance than earlier tests. Although remission criteria had been not respected, a global improvement was detected by BPRS, SAPS and SANS. Scores were unsatisfactory in items linked to positive symptoms, especially for auditory hallucinations (scores worse than "mild" in every scale).

Discussion

Our patient was considered strongly refractory to drug therapy. According to NICE guidelines [18], she showed inadequate response to at least two antipsychotic drugs (one of the drugs being a non-clozapine SGA) at the maximally tolerated dose within the recommended therapeutic range, in trials lasting six weeks or more [17,4,6], before starting a clozapine trial [18]). Clozapine shows low interaction with dopaminergic D2- and D3-receptors and high affinity towards serotonergic 5-HT2A, 5-HT2C, 5-HT6,

5-HT7, dopaminergic D4, muscarinergic m1- and alpha-1-adrenergic receptors [19]; it remains the most effective drug in non- responsive patients [9] and the only evidence-based medication for treatment-resistance schizophrenia [6].
Although clozapine is the third and last line therapy, up to 40% of previously treatment-refractory patients do not reach a satisfying functional recovery [20-22] and some patients have poor or partial response during clozapine monotherapy [23]. Moreover, some patients should be considered clozapine-intolerant because of the severity of side effects: reversible (but potentially fatal) agranulocytosis requires interruption for clozapine administration, while sedation, fatigue, psychomotor retardation, sialorrhea, metabolic (weight gain, dyslipidaemia) and cardio-metabolic abnormalities need clozapine dose reduction [23-26].
Furthermore, clozapine may induce obsessive-compulsive syndromes [27,28] and seizures and these condition requires dose reduction or a combination strategy [29,30]. Our patient showed several side effects at the beginning of clozapine trial, which prevented an adequate compliance. In order to improve her clinical and psychological conditions, a combination strategy was applied: aripiprazole was added in order to supplement clozapine anti-dopaminergic properties [31]. The antipsychotic selection was based on some evidence that suggest to add to clozapine a second-generation antipsychotics (such as sulpiride, amisulpride, aripiprazole, ziprasidone and risperidone) [32,21,33] in order to prevent serious extrapyramidal and other side effects produced by the combination with first-generation antipsychotics [34]. Due to clinical trials, case reports and literature reviews [19,34-36] suggesting the efficacy of combined clozapine-aripiprazole treatment, Aripiprazole was selected as add-on therapy in our patient. Pharmacokinetic and pharmacodynamic complementary nature of clozapine-aripiprazole might not cause significant interactions. In fact Aripiprazole is mainly metabolised by hepatic cytochrome P-450 CYP 2D6 and 3A4 isoforms, while CYP 1A2 is the major enzyme metabolising Clozapine [37]. This drug acts as an antagonist of positive symptom-related mesolimbic dopaminergic pathways and, conversely, works as a functional agonist of the mesocortical, negative symptom-associated dopaminergic pathways. Aripiprazole is a D2 dopamine receptor partial agonist that shows a neuroreceptorial profile complementary to clozapine, while its partial agonism at 5-HT1A receptors improves anxiety, negative depressive symptoms and especially cognitive dysfunctions, with interesting results in refractory patients [38]. Furthermore add-on therapy with Aripiprazole allows to reduce clozapine dose and improves side effects [34,39]. In addition to side effects preventing a good compliance, A. showed poor response to clozapine: also with a greater dose of drug (250 mg/day) the improvement in positive symptoms was inadequate. Considering that greater dose causes larger side effects, we preferred to administer lower dose of clozapine (175 mg/day) and to combine psychosocial interventions. In fact, an alternative way to treat schizophrenic patients is based on psychosocial intervention strategies: a mixture of medical, social (community and family based intervention), and psychological (especially Cognitive-Behaviour Therapy) interventions aimed at the social integration of the patients [7]. Although there is little evidence assessing the efficacy of combining pharmacological treatments and psychosocial interventions, for many years psychosocial interventions have been a core features of the management of schizophrenia, regarded as essential and integral part of the treatment [40]. Evidences based on clinical practice suggest that a combination of psychotherapy, family therapy and occupational therapy could enhance the effects of pharmacological treatments [41], especially when used in early psychosis [42], and could be effective in the treatment of resistant schizophrenia [43]. Moreover, the updated edition of the schizophrenia guideline recommends psychotherapies and family interventions in acute episode of schizophrenia and in patients with established schizophrenia [6]. There is little evidence about psychosocial interventions in drug-resistant schizophrenic patients, although many studies confirmed the importance of a combined treatment in schizophrenic population. Short-term benefits of psychosocial intervention have been well demostrated in Lieberman's review of literature about early interventions in first episode psychosis, although there is no evidence about long-term improvement in social/occupational disability due to psychosocial interventions delivered early in psychosis [15]. A recent systematic review had found evidence that CBT reduces symptom severity in early and established psychosis but does not effect relapse rates, while family intervention reduces combined hospital admission and relapse rates [42]. At the same time evidences that family interventions combined with individual CBT increase time to relapse have been found, although no effects on relapse rate could be proved [43]. Moreover, cognitive remediation therapies had been shown to improve cognitive, motivational and emotional difficulties, and real world functioning in patients with schizophrenia [44]: CRT combined with other psychosocial interventions could enhance functional outcomes. As it is known, effects of psychosocial interventions could be appreciated after a long period of observation [15]. This may be the reason why we could not observe a sudden improvement in our patient.
Andreasen's working group consensus defined remission as a score of mild, or better, simultaneously on all items of BPRS, or SAPS and SANS, during a period of at least 6 months [4]. Remission criteria were not respected in our patient nine months later the first access to the Daily Center: SAPS showed scores higher than 2 points (corresponding to "mild") in 9/34 items (Tab. I), SANS scores were higher than 2 in 7/25 items (Tab. II), while BPRS scores were worse than mild in 6/18 items (Tab. III). On the other hand, a global improvement of A. performance was noted by the HONoS Rome assessment (there was an improvement in all the items of the HONoS Rome, with the only exception of "Family members' collaboration")

Table I. SAPS.

SAPS	T0 (23-06-2016)	T1 (23-03-2017)	Total score difference
Hallucinations			
Item 1: auditory hallucinations	4	4	0
Item 2: voices commenting	4	4	0
Item 3: voices conversing	4	4	0
Item 4: somatic or tactile hallucinations	0	0	0
Item 5: olfactory hallucinations	0	0	0
Item 6: visual hallucinations	0	0	0
Item 7: global rating of hallucinations	4	3	1
Delusions			
Item 8: persecutory delutions	2	0	2
Item 9: delusions of jealousy	0	0	0
Item 10: delusions of guilt or sin	2	0	2
Item 11: grandiose delusions	1	0	1
Item 12: religious delusions	0	0	0
Item 13: somatic delusions	2	0	2
Item 14: delusions of reference	2	0	2
Item 15: delusions of being controlled	1	0	1
Item 16: delusions of mind reading	1	0	1
Item 17: tought broadcasting	1	0	1
Item 18: tought insertion	1	0	1
Item 19: tought withdrawal	1	0	1
Item 20: global rating of delusions	2	0	2
Bizarre behavior			
Item 21: clothing and appearance	4	3	1
Item 22: social and sexual behavior	0	0	0
Item 23: aggressive and agitated behavior	3	0	3
Item 24: repetitive or stereotyped behavior	2	2	0
Item 25: global rating of bizarre behavior	2	2	0
Positive formal tought disorder			
Item 26: derailment	4	4	0
Item 27: tangentiality	4	4	0
Item 28: incoherence	3	2	1
Item 29: illogicality	3	3	0
Item 30: circumstantiality	2	2	0
Item 31: pressure of speech	1	0	1
Item 32: distractible speech	3	3	0
Item 33: changing	0	0	0
Item 34: global rating of positive formal thought disorder	3	3	0
Tot.	66	43	2

(Tab. IV). In fact, in spite of the persistence of auditory hallucinations, A. became able to manage these voices with the help of the Mental Health Daily Service operators. Through the family interventions, a good participation of her parents had been obtained: this allowed us to achieve a better compliance to pharmacological therapy, reducing effects due to discontinuation use of drugs. Despite the persistence of auditory hallucinations, RCT allowed A. to attend her university class with a medium performance. Also daily functioning and social skills improved.

Table II. SANS.

SANS	T0 (23-06-2016)	T1 (23-03-2017)	Total score difference
Affective flattening or blunting			
Item 1: unchanging facial expression	0	0	0
Item 2: decreased spontaneous movements	0	0	0
Item 3: paucity of expressive gestures	0	0	0
Item 4: poor eye contact	0	0	0
Item 5: affective non responsivity	3	1	2
Item 6: inappropriate affect	4	2	2
Item 7: lack of vocal inflections	0	0	0
Item 8: global rating of affective flattening	2	1	1
Alogia			
Item 9:poverty of speech	0	0	0
Item 10: poverty of content of speech	0	0	0
Item 11: blocking	2	0	2
Item 12: increased latency of response	3	0	3
Item 13: global rating of alogia	3	0	3
Avolition/apathy			
Item 14: grooming and hygiene	4	3	1
Item 15: inpersistence at work or school	5	3	2
Item 16: physical anergia	2	0	2
Item 17: global rating of avolition/apathy	5	4	1
Anhedonia/asociality			
Item 18: recreational interests and activities	3	0	3
Item 19: sexual activity	4	0	4
Item 20: ability to feel intimacy and closeness	5	4	1
Item 21: relationships with friends and peers	5	4	1
Item 22: global rating of anhedonia/asociality	5	3	2
Attention			
Item 23: social inattentiveness	5	3	2
Item 24: inattentiveness during mental status testing	4	0	4
Item 25: global rating of attention	5	3	2
Tot.	69	31	38

According to Lieberman [45], our patient satisfied Criteria for Functional Recovery from Schizophrenia: she presented a good illness self-management, she was able to participate in recreational activities organized by the Daily Center or with family's members, she was improving in independent living skills, in relations with family and in academic performance. In order to prove the regular assumption of the drug therapy, according to literature [16,46-54] we tested the plasma levels of clozapine. This exam could be useful also to explore patient metabolism, involved in the sensitivity to the drug. There is no concordance among studies evaluating clozapine plasma levels: no clear therapeutic interval has been established. Some studies suggest plasma levels higher than 350 ng/ml for clozapine resistant patient. Unfortunately this range is linked to an increased rate of side effects [16,46-54]. Clozapine plasma level in our patient was of 170 ng/ml. This level is considered too low to define resistance to clozapine in schizophrenic patient, but we were unable to increase the dose without worsening side effects and causing distress in the patient.

Conclusions

Schizophrenic patients who do not respond or are considered intolerant to drugs could benefit from psychosocial interventions. Nowadays, the mean goal of schizophrenia treatment seems to be symptomatic remission, that is often achievable only through several pharmacological trials. More often drugs could be

Table III. BPRS.

BPRS	T0 (23-06-2016)	T1 (23-03-2017)	Total score difference
Item 1: somatic concern	5	3	2
Item 2: anxiety	6	5	1
Item 3: emotional withdrawal	4	2	2
Item 4: conceptual disorganization	6	5	1
Item 5: guilt feelings	6	5	1
Item 6: tension	6	5	1
Item 7: mannerisms and posturing	4	3	1
Item 8: grandiosity	2	2	0
Item 9: depressive mood	6	1	5
Item 10: hostility	3	1	2
Item 11: suspiciousness	5	3	2
Item 12: hallucinatory behavior	6	6	0
Item 13: motor retardation	4	1	3
Item 14: uncooperativeness	3	1	2
Item 15: unusual thought content	5	4	1
Item 16: blunted affect	3	3	0
Item 17: excitement	3	3	0
Item 18: disorientation	2	1	1
Tot. (?)	79	54	25

Table IV. HoNOS-ROMA.

HoNOS-Roma	T0 (23-06-2016)	T1 (23-03-2017)	Total score difference
Item 1: deliberately self-harm thoughts or behavior	1	0	1
Item 2A: hyperactive, aggressive, destructive and agitated behaviors	2	0	2
Item 3A: abuse of alcohol or drugs or other addictions, such as gambling	0	0	0
Item 4A: memory, orientation, understanding and thought disorganization	3	1	2
Item 5A: problems (organic / physical / somatic)	1	0	1
Item 6A: hallucinations and delusions	3	2	1
Item 7: depressed mood	2	1	1
Item 8A: other psychological symptoms	3	2	1
Item 9A: relationships with the outside world (family members, partners, friends)	3	2	1
Item 10a: social relationships	4	3	1
Item 11: autonomy in everyday life	3	2	1
Item 12A: work, study or other equivalent activities	4	3	1
Item 13: financial and housing conditions	NV	2	
Item 14: family load	3	2	1
Item 15: enviromental opportunities where he/she lives	0	0	0
Item 16: family members' collaboration	1	1	0
Item 17: case management problems	2	1	1
Item 18: patient's ability to cooperate and to define aims and commitment to achieve them	3	2	1
Tot.	37	24	16

intolerable for patients, due to important side effects. Anyway, these difficult to treat patients could achieve functional and social outcomes thanks to psychosocial interventions combined with a pharmacological approach that should be more tolerable for them, although less effective against symptoms. It is possible that a good

Table IV. HoNOS-ROMA.

HoNOS-Roma(FACE)	T0 (23-06-2016)	T1 (23-03-2017)	Total score difference
Item 1: AL- eating disorders symptoms	1	0	1
Item 2: AN-anxiety, phobias and panic	3	2	1
Item 3: DI-dissociative symptoms	2	1	1
Item 4: MA-high mood and ideation	0	0	0
Item 5: OC-obsessive symptoms and compulsions	0	0	0
Item 6: SE-sexual disorders symptoms	NV	2	
Item 7: SO-sleep disorders	3	1	2
Item 8: SS-somatoform symtoms, somatic and hypochondriacal concerns	1	0	1
Tot.	10	6	4

functional recovery, even supposing a partial or incomplete remission, could bestow to these patients a good quality of life, thats hould be the aim of every psychiatri cand medical intervention. This latter should be object of further studies.

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