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Treatment Principles of First-Episode Psychosis

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ABSTRACT

Treatment of first-episode psychosis, which has unique advantages and challenges, has an impact on the course of the illness. On one hand, clinician has to understand triggering factors of psychosis and make differential diagnosis, and on other hand he has to choose a rationale psychopharmacological treatment. Although there is no difference between first generation antipsychotics and second generation antipsychotics in terms of effectiveness, the latter group has advantages in terms of side effects and tolerability. Tolerability issues and particularly metabolic side effects should be taken into account when choosing antipsychotic to treat first episode and beyond. Additionally, psychosocial approaches like family psychoeducation should be combined with pharmacological approaches in early phase of psychosis. Clinicians should monitor the medication adherence in every outpatient visit, and minimum duration of treatment is recommended as three years after remission.

Keywords: First-episode, psychosis, pharmacological treatment, psychosocial treatment

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INTRODUCTION

This paper discusses the treatment approaches during the first episodes of individuals diagnosed with schizophrenia, schizoaffective disorder, brief psychotic disorder, other psychotic disorder or substance-induced psychotic disorder. This approach requires inclusion of multidimensional interventions beyond the question "Which antipsychotic should we use in which dose and for how long?". Interventions for differential diagnosis and non-pharmaceutical interventions should be used relatively more compared to patients who experienced many episodes. Patients with schizophrenia who are experiencing their first episode within a year comprise a small portion, approximately 2%, of the entire population of patients with schizophrenia. Psychiatrists may not, therefore, feel competent in the treatment of this group which they rarely encounter in their daily routines. The first psychotic episode is an unexpected and usually frightening experience for the patients and their relatives. The ill person usually meets a psychiatrist and other psychiatric staff unwillingly for the first time in this period. Investigation of the first psychotic episode provides important advantages for the understanding of schizophrenia and related psychotic conditions. Investigation of this period is an opportunity to understand the behaviour patterns or symptoms that we observe in patients with chronic psychosis and think to be associated with the effects of long-term antipsychotic use, social isolation or multiple exacerbations. The number of studies that have searched this subject in PubMed has increased almost two fold in the last five years reaching 6175 as of August 2020.

WHERE AND HOW SHOULD A PATIENT WITH FIRST-EPISODE PSYCHOSIS BE MONITORED?

Ideally, the patients in this group should be monitored in the units specialised in the treatment of schizophrenia or they should be referred to such units. A meta-analysis assessing the effectiveness of the interventions towards preventing a second exacerbation after the first-episode has reported that the rate of exacerbations was lower in patients treated in centres specialised in treatment of first-episode psychosis and the results obtained with cognitive behavioural therapy were not any better than the results achieved in these centres (1). When we compared the exacerbation and rehospitalization rates of the first 20 patients we monitored in the Istanbul School of Medicine, Psychotic Disorders Research Program with those of the next 60 patients, we found a significant difference. We observed that with increasing experience in the area, the chances of success increased even within the same centre. Considering the status of routine outpatient clinic services in Turkey, it is known that the time devoted to a patient does not usually exceed ten minutes. It is a time consuming process, however, to assess a young patient presenting with psychotic symptoms and establish a differential diagnosis. If the circumstances allow, it will be very useful to examine the patient at the inpatient clinic even for a period of a few days before arriving at a final diagnosis. It would be appropriate to deprive the patient of drugs for some time during such examination. It may be thought that hospitalization of a young patient who is not likely to harm self or others at this stage will lead to unnecessary stigmatization. It should be kept in mind, however, that the patient will bear the label of a schizophrenia diagnosis made hastily and the possible effects of the treatment towards such "diagnosis" lifelong. Taking into consideration the circumstances in our country, it seems more realistic that persons to be treated after their first episode are monitored by the same physician if not in a special unit, are provided with psychological support during treatment and more cooperation is established with their families.

WHAT TO CONSIDER IN DIFFERENTIAL DIAGNOSIS?

Making the differential diagnosis is more important than selecting treatment in first psychotic episode. It should be kept in mind that

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mood disorders with psychotic features as well as psychotic conditions associated with substance use or medical reasons can be confused with schizophrenia in young patients. This issue is so important to be the subject of a separate paper; we can only mention some main topics here. Bipolar disorder and schizophrenia have similar prevalence. Moreover, the first manic episode seen in a young patient will most likely involve also psychotic features. On the other hand, the prevalence of depression is higher. The likelihood of depression should not be overlooked in a young patient showing psychotic symptoms (even if delusions or hallucinations not congruent with mood are present). In the differential diagnosis of schizophrenia and mood disorders, the classical knowledge underlines the importance of the nature of the symptoms predominating the condition (psychotic symptoms/mood changes), the presence of schizophrenia/mood disorders in the family history, how the patient responds to what drug group (antipsychotics/mood stabilizers) particularly in the exacerbation period, and whether or not the patient remains well without drugs. However, we see in practice that all of these may be misleading. The most reliable method to make the differential diagnosis between schizophrenia and mood disorders is to monitor the patient regularly for at least a year and assess a number of parameters such as functioning and disability. It will be helpful to keep this fallibility in mind even in cases when you are very certain about the initial diagnosis. Such diligence will not make us lose anything but may contribute a lot to the patient's life.

We know that when making a differential diagnosis for schizophrenia we should pay particular attention to the reasons associated with the general medical condition in patients outside the usual age interval. Patients 17 years of age and younger also fall in this group, which is defined as early-onset schizophrenia. Use of brain imaging methods, electroencephalography (EEG) and extensive biochemical tests should be part of routine examinations in these patients. The condition of encephalitis caused by anti-NMDA (N-methyl-D-aspartate) antibodies, which has become a current issue recently, should also be considered especially in young female patients who show symptoms of psychosis for the first time. A recent study found Anti-NMDA antibody positivity in 3.5% of 112 patients with first episode psychosis, but only one patient was diagnosed with encephalitis (3). It was also reported that this diagnosis needed to be supported by EEG and magnetic resonance imaging results and a patient who did not have antibodies in their cerebrospinal fluid (CSF) was, in fact, diagnosed with anti-NMDA encephalitis based on these results (4). Also in our clinic, a young patient who had been hospitalized due to psychotic symptoms continuing for a few months and whose EEG had been considered within normal limits 6 months ago was later diagnosed with SSPE (Subacute Sclerosing Pan-Encephalitis) as a result of additional examinations (5). In the aetiology of first-episode psychosis, the major findings that would suggest causes associated with the general medical condition include presence of physical symptoms such as high fever that occur before or concurrently with psychiatric symptoms, the psychiatric symptoms being atypical, the patient being young, and failure to obtain the response expected from the initial treatment (even worsening of the condition).

The prevalence of alcohol-substance use among patients with schizophrenia ranges between 20 and 70% in Western societies. This problem has obviously become increasingly important also for our country. While in 90 s schizophrenia and substance use or substance related psychosis was seen only in young people coming from abroad, these conditions have become more widespread in recent years. In first-episode psychosis, it is absolutely necessary to question substance use, and if required, to perform substance metabolite testing in the urine regardless of the patient's sociocultural or economic status. With the increase in the use of synthetic cannabinoids recently, it has become more important to differentiate between substance induced psychosis and the comorbidity of schizophrenia and substance addiction. Remission of psychotic symptoms when substance use is discontinued for about three months may suggest that the first diagnosis is more likely. However, continuation of substance use disorder in most cases makes things more complicated. In cases of substance induced psychosis –at least during the first episode– cognitive and negative symptoms seem to be less compared to patients with schizophrenia.

Finally, individuals who have not satisfied the psychotic disorder criteria at syndrome level yet but carry the risk of progressing towards psychosis if left alone should also be considered in differential diagnosis. Defined as the psychosis risk syndrome or risk group for psychosis, this group is characterised by psychosis-like experiences at a sub-threshold level or of a severe but shortly subsiding nature. The persistence status of psychotic symptoms is more determinative in the differential diagnosis. If there is spontaneous remission in psychosis-like experiences in a period less than a week, the person should be included in the group carrying the risk of psychosis rather than being diagnosed with schizophrenia. It should be kept in mind that such persons may also be diagnosed with other psychotic disorders (defined or undefined).

PRINCIPLES OF TREATMENT

The treatment principles of the first-episode are specific in a number of ways. Most probably, the patient has come to know about psychiatric treatments for the first time. It is generally agreed that the response to treatment in patients with first-episode psychosis is better than in those with multiple episodes. Knowing that treatment response is quicker and more favourable in the first period provides incentive to use this opportunity in the best way. It can be said that the first-episode is a "window of opportunity" for the intervention to the psychotic phase. A 3–6 month delay may result in the loss of this chance of positive response. Treatment response to positive symptoms is known to be better.

In the First-Episode Follow-Up Study of Istanbul Medical School, 59.5% of the patients were able to meet the severity and duration criteria of remission within the first 24 months (6). A recent meta-analysis has reported that 81% of 3151 first-episode patients met the 20% decrease criterion in the PANSS (Positive and Negative Syndrome Scale) or the BPRS (Brief Psychiatric Rating Scale). However, it should be noted that a decrease at this level indicates only a limited remission and can be achieved even with the alleviation of anxiety-related symptoms alone (7). The proportion of those who met the 50% decrease criterion in the scales, which indicates a more significant clinical response, was 52%. The response was observed to be better in female patients and those who had severe symptoms at the beginning, had not used antipsychotics before, and had a short treatment-free psychosis period. There was less efficacy in the remission of negative symptoms alongside positive ones (7). In a 7-year first episode follow-up study, the proportion of those achieving remission in both symptoms groups was only 29% (8).

One point on which all studies investigating post-first episode progression have agreed is that treatment nonadherence almost invariably leads to exacerbation. In our series, treatment nonadherence was 70% in patients who had exacerbations within a year following the first-episode and 25% in those who had no exacerbations (9).

This period in which the chance of benefiting from treatment is the highest is paradoxically also the period in which the patient and even their relatives are most reluctant to accept the diagnosis and cooperate in the treatment. For this reason, the patient and their family should be provided detailed information about the nature of the disease, factors effective in preventing exacerbations, what to expect from the treatment, and what to be careful about in treatment. An explanation to be made by the physician can be so significant that the course of the patient's life may change.

Families of patients bringing their patient for the first time to a psychiatrist due to psychotic symptoms usually ask these questions: "Is it schizophrenia?" or "It is not schizophrenia, is it?" For the reasons we discussed before, the physician is not in the position to give a clear answer to this question. If we have an initial diagnosis in mind, we would think this at the same time: "Should I say it or shouldn't I, what should I say?" Whatever we say, it is important to give a straightforward and clear message to the relatives of the patient. It is appropriate and necessary to say that the patient is going through or has gone through a psychotic period. It will be enlightening for the patient's relatives to explain this by giving examples from the positive symptoms of the patient. Telling them that the acute symptoms of the first-psychotic episode will alleviate with treatment no matter what the diagnosis may be, will also relax patient's relatives and encourage them to cooperate. Another general fact to share with patient's relatives is that the patient's progress after the first-episode will largely depend on his/her compliance with the medication and treatment. If we see that the patient's relatives have a realistic approach and schizophrenia is a possibility for the patient, it will be appropriate to mention during the conversation that schizophrenia is among the possible diagnoses but we will be able to give a more precise opinion about the diagnosis during the follow-up process which may take 5–6 months. Briefly, the information we will provide sparing 5–10 minutes of our time will most probably eliminate the worries of the family and convey the message that we are concerned about their patient. Our message should involve neither unnecessary optimism nor unnecessary pessimism. It may be necessary to repeat the same words a few times in the face of the objections of the patient's relatives that may at times reach as far as denial. Generally, families have the tendency to blame themselves. "Were we too late, did it happen because we behaved that way?" These questions should be answered in a way to eliminate the worries of patient's relatives. Whatever we do, some of the relatives of the patient may still seek another physician who will make things look brighter for them.

PSYCHOSOCIAL THERAPIES

The place of psychosocial therapies in texts on the treatment of schizophrenia usually comes after conventional pharmacological therapies. Although we agree that the pharmacological approach is at the centre of the treatment also for the first-episode, we start from psychosocial therapies to emphasize that they are as necessary and useful as medicines. We know that the aetiology of schizophrenia involves more than one cause. Therefore, the causes that make an individual come to us with schizophrenia as a phenotype that make up the last straw, are more than one. Genetic, neurodevelopmental events, pathologies of neurotransmitters and receptors, and psychosocial causes have combined most of the time. If we can reverse these causes that make the individual pass beyond the threshold making him/her "psychotic", then it will also be possible for us to reverse the psychosis. We do not have the possibility to repair genetic and neurodevelopmental causes at the present time. We try to control the disorders found in neurotransmitters and receptors, which we assume to be associated with schizophrenia, at a symptomatic level using the drugs available to us. The variables causing psychosocial stress (if they do not initiate the disease) comprise the group for which our chances of intervention are the highest at least to alter the progression of schizophrenia. We can include many things in this group, from the person's problem solving and communication skills to their emotion expressing level in the family, from interaction of family members with each other to the patient's role in the family. An approach to regulate in-family communication channels in selected patients can break the vicious circle in which the physician is trapped. Moreover, families desperately ask how they should treat their ill member. The ideal solution to this may be 5–6 hour informative meetings in a multiple family group format. These education group meetings, which we also hold in our clinic from time to time, are being very useful particularly in regulating expressed emotions. We invite almost all of the patients who take part in the first-episode follow-up project to participate in psychosocial treatment groups that are being held in the clinic. Our general impression is that when a patient learns the ways to establish relationships with surrounding people and how to solve problems, this protects them against exacerbation. A recent study has reported that approaches focusing on recovery after the first-episode increase treatment motivation (10).

It is a known fact that psychosocial therapies for the patient or psycho-education for the families are very rare, if any in our country. However, if we wish to treat young patients with schizophrenia in a more effective way, we have to create such psychosocial therapy opportunities for groups as a minimum.

Physical Exercise

Data have accumulated in recent years showing that physical exercise has positive clinical effects not only on depression and anxiety but also on patients with psychosis. It was reported that the positive symptoms of the patients who participated in an exercise program after the first-episode decreased compared to the control group and while the negative symptoms increased in the control group, there was no such increase in the exercise group (11). Exercising was thought to show this effect by reducing oxidative stress and balancing the antioxidant system. As an activity with no side effects and a positive impact on the economy and general health, exercising should be recommended for all psychotic patients and questioned during subsequent interviews.

PHARMACOLOGICAL TREATMENTS

Irrational treatments in chronic patients that we often see in daily practice also occur after the first-episode. In the RAISE (Recovery After an Initial Schizophrenia Episode) study conducted with the public support in the United States of America, it was found that immediately after the first-episode, high-dose antipsychotics were prescribed in 8.8% of the patients, mostly high-dose olanzapine in 32%, more than one antipsychotic in 23.3%, antidepressants without any understandable reason alongside antipsychotics in 36.5%, psychotropic drugs not containing antipsychotics in 10.2%, and psychostimulant drugs in 1% (12).

Is Antipsychotic Selection Important in the Treatment of First-Episode?

The characteristics of the patient (nature of major symptoms), the properties of the drug, and the history of the patient (what drugs used previously, what their benefits were, etc.) should guide us when selecting an antipsychotic to treat schizophrenia. Considering that a considerable portion of the first-episode schizophrenia patients have not used any drugs previously, the general characteristics of drugs will play a major role in selecting an antipsychotic.

A meta-analysis dated 2010 found that the rate of exacerbation was lower in patients using the second-generation antipsychotics (OR: 1.47) than in those using the first-generation antipsychotics (13). A meta-analysis published in 2017 (14) has reported that the second-generation drugs were superior to haloperidol in the treatment of first-episode psychosis, but the difference between them was limited. In that study, amisulpride was found more effective than quetiapine in general and olanzapin was found superior to risperidone and haloperidol in the treatment of negative symptoms. It is recommended, therefore, to consider side effects as one of the priorities when selecting an antipsychotic. It should be noted in this context that aripiprazole, quetiapine, risperidone and ziprasidone were specified in the RAISE study conducted in the USA with public support as the first choice drugs in the treatment of first-episode psychosis. Olanzapine, haloperidol, clozapine and chlorpromazine are in the group of drugs of second choice in the study protocol (15). In an open randomized study

dated 2020, any one of olanzapine, risperidone, aripiprazole, quetiapine, ziprasidone and haloperidol was started to the patients with first-episode psychosis (n=376) and the period of medication adherence was used as the outcome criterion. As a result, aripiprazole, olanzapine and risperidone were reported to be advantageous in terms of efficacy (16).

It is important to see if there is any difference with respect to 3 points between these groups when choosing a first/second generation antipsychotic: 1. Side effects, 2. Patient satisfaction with the drug and 3. long-term prognosis of the disease. The ability of an antipsychotic drug of choice to show the most favourable effect on disease prognosis is important in that the patient who is introduced to an antipsychotic drug for the first time will not have a negative impression as far as possible about that drug, which may have to be used for a lifetime. A magic solution to meet all these criteria though seems to be non-existent, at least for now. Nevertheless, let us take a look at the statuses of the first/second generation drugs with respect to the above 3 areas based on available data.

As for side effects, the first generation antipsychotics are known to carry the risk of developing tardive dyskinesia (TD) in the long run, whereas the second generation drugs have a low TD risk. Yet, the metabolic side effects of the second generation drugs may pose problems in young patients even in the early period of the treatment. Based on available trial results, olanzapine is not recommended as the first line treatment in adolescents diagnosed with schizophrenia due to risk of weight gain and diabetes (17). A study dated 2020 has reported that in first-episode schizophrenia patients who have never used antipsychotics before, insulin resistance occurred in the second week of the treatment and the HDL cholesterol level dropped in the fourth week (18). These data suggest that the risk of metabolic side effects is a major variable in the selection of the first drug.

We can assume that the drug to be chosen for the f, rst-episode will also be used in the maintenance treatment. Functioning and cognitive capacity seems to decline in time in most of the patients treated with first generation drugs. The data on the effect of the second generation drugs in this area are not adequate. However, if we are to select a drug when starting the treatment, it would be appropriate to start the treatment with the second generation drugs taking into consideration the limited benefits of the first generation drugs in the first-episode. It is appropriate to use the classical antipsychotics in patients who need parenteral treatment and in those who exhibit expansiveness/aggression.

Antipsychotic Drug Dosages

Compared to a patient with schizophrenia exhibiting recurrent episodes and a chronic course, lower doses of antipsychotics will suffice to control the initial period. In the 2009 update of the PORT (the Schizophrenia Patient Outcomes Research Team) report, the first generation antipsychotics are recommended in a dose equivalent to chlorpromazine 300–500 mg/day for the treatment of first-episode and an initial dose of the second generation antipsychotics equal to a half of the lower limit of the dose range required for the patients with a history of multiple episodes. It is stated as a major exception to this that the dose may need to be increased up to 400–500 mg/day for quetiapine (19).

Place of Long-Acting Injectable Antipsychotics in First-Episode and Thereafter

The long-acting injectable forms of antipsychotics are recommended as a solution to prevention of exacerbations associated with incompliance with medication. There are studies showing that this form is more effective in preventing exacerbations or hospitalization in the early period of the disease compared to oral antipsychotics (20). Long-acting injectable antipsychotic use may be decided for patients who discontinued at least two antipsychotic drugs due to incompliance as well as for young patients who benefited from oral therapy in the treatment of their first-episode while at the hospital but stated that they would stop their medication after discharge. Since substance use often relates to lack of insight, it should be kept in mind that the patients in this group will also fail in medication compliance. In a recent study, 21% of first-episode patients who responded well to treatment at the beginning were reported to experience exacerbations in their two-year follow-up period (21). That study also reported that patients whose positive symptom severity was low and social relationships were weak at the beginning were at risk. These results, however, indicate that long-acting antipsychotics alone are not sufficient in preventing exacerbations and psychotherapeutic support would also be needed.

Duration of Treatment After First-Episode

Although remission is seen in a large majority of patients after the first psychotic episode, it is common to experience exacerbations in the course of schizophrenia in the long term. Most of the previous treatment algorithms emphasize that at least a year of uninterrupted antipsychotic therapy is needed to minimise relapses (22). We can talk about some rational reasons for setting a limit of one year. Only a small group of schizophrenia patients are known to exhibit full remission after the first-episode and to be able to sustain their well-being free of medication thereafter. The goal in the Istanbul School of Medicine First-Episode Follow-Up Program was to gradually decrease and then discontinue antipsychotic drugs in patients who completed a year of treatment without experiencing exacerbations, who are stable and have not described any life event that may be a source of stress in the future. The antipsychotic therapy was discontinued in 16% of the 105 patients who satisfied these criteria, but psychotic exacerbations were seen in 58% of these patients in the medication free follow-up period (23). We can conclude that about 6% of the patients in this program did not experience exacerbations after the cessation of their antipsychotic treatment. These results suggest that discontinuation of antipsychotic treatment after the first-episode is possible only in a limited patient group, but a high rate of exacerbations may still occur even in this group. Two measures may be taken to reduce this and increase the percentage of patients who will not experience exacerbations. A recent article mentions three options, keeping an antipsychotic therapy perpetually after the first-episode, discontinuation of the therapy after a two-year use, or waiting at least three years for this (24). The first option does not seem appropriate due to undesired effects and rejection of the patient and their relatives. As in our study, other studies also report high rates of exacerbations when medication is stopped after one or two years of treatment. In this case, it seems reasonable to wait at least three years before an antipsychotic therapy is discontinued in selected patients.

The second measure to reduce the risk of exacerbation in the process of antipsychotic cessation is to discontinue the medication at a rate even slower than proposed in the usual protocols. An article dated 2020 has reported that spreading the antipsychotic cessation process over a period of 4 weeks was no different from immediate cessation, but spreading drug cessation process over 3–9 months reduced the exacerbation rate by a half (25). It is recommended to consider receptor involvement rates when reducing the dose of an antipsychotic. For example, when decreasing risperidone from 10 mg to 1 mg, there is a drop in receptor involvement by 38%, whereas when decreasing it from 1 mg to 0 mg, a 44% drop occurs. It seems appropriate to follow very low decrements such as 0.5, 0.25 or 0.125 mg divided over months when discontinuing risperidone (25). It may be appropriate for a physician to plan reducing and then stopping the treatment after an adequate antipsychotic therapy following the first-episode also in cases when he/she is not certain about the diagnosis of schizophrenia. Although schizophrenia is a disorder with a high diagnostic consistence, this may not be the case within a year following the first-episode. It is not rare that some patients would receive a mood disorder diagnosis in the follow-up period.

PLACE OF ELECTROCONVULSIVE THERAPY DURING FIRST-EPISODE

Treatment algorithms do not mention electroconvulsive therapy (ECT) in the first-episode. However, it can be considered as a treatment option particularly in patients carrying the risk of harming self and others. ECT is used more in patients with "first-episode psychosis" which includes possible psychotic mania conditions rather than in patients with first-episode schizophrenia. We saw that ECT was administered to 13 patients (15%) in the first-episode in our patient group. Most of these patients were not included in the paranoid subtype. While ECT was administered as the first choice to the patients in the catatonic subtype, the others received it after lack of response to antipsychotic treatment or destructive behaviour to self/others. These patients had shorter treatment-free psychotic period than the other patients and their BPRS and SANS (Scale for Assessment of Negative Symptoms) scores were higher at the time of admission to the hospital, for which catatonic patients may be responsible. Their BPRS scores at the time of discharge from the hospital were, however, lower than those of the group that did not receive ECT. No difference was found between one-year exacerbation rates of the patients who received and did not receive ECT (26). ECT can be said to be an effective option in the first-episode in patients who cannot benefit from drug therapies and in catatonic and disorganised patients.

In conclusion, we can say that achieving remission will be a realistic goal in the treatment of first-episode schizophrenia, but the problem of medicine incompliance should not be overlooked even if remission has been achieved.

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