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Pharmacotherapy of Schizophrenia in Acute and Maintenance Phase

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ABSTRACT

Schizophrenia is one of the leading disorders causing impairment in society. Therefore, it is crucial to review evidence-based treatment approaches which are both effective and causing minimum side effects. In this paper, treatment recommendations for first episode schizophrenia, patients in acute phase with a history of multiple episodes, and patients in the maintenance phase will be discussed in light of the Psychiatric Association of Turkey Guideline for Treatment of Schizophrenia, other recent national and international guidelines as well as expert consensus reports in the literature. Finally, practical considerations will be suggested.

Keyword: Schizophrenia, psychotic disorders, drug therapy

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INTRODUCTION

Studies conducted in Turkey showed that the lifetime prevalence of schizophrenia is approximately 1% in the general population (1, 2). This rate rises to 2.5% when other mental disorders with psychotic features are also taken into account (2). About a half of these patients, in other words 1% of the adult population are permanent users of health services due to psychotic symptoms (1, 3). According to the data of Turkish Ministry of Health, schizophrenia and related disorders are in the 9th place among the illnesses that lead to disability (4). These results highlight the importance of effective treatment for schizophrenia and related disorders.

Recent studies suggest a staging model for psychotic disorders. According to this model, psychotic disorders may appear with different presentations including the following periods: non-specific symptoms, a high risk period, first episode psychosis, psychotic relapses or permanent symptoms in individuals with previous diagnoses and treatment resistance (5). In this review, pharmacotherapy of first episode schizophrenia, acute relapses in individuals with previous diagnoses and the maintenance phase are going to be reviewed in light of the updated evidence as well as the current guidelines.

METHODS

For this review, we searched for articles published between 01.01.2004 and 22.07.2020 in Turkish or English using the online databases of PubMed and Google Scholar. The search terms used were "schizophrenia guidelines" and "schizophrenia psychopharmacology". Guidelines and consensus reports including recommendations for the pharmacotherapy of acute and maintenance phases of schizophrenia were reviewed in detail. Furthermore, the reference list of these papers was manually searched. No exclusion criterion was applied. Finally, recommendations in the second edition of the Schizophrenia Treatment Guideline of Psychiatric Association of Turkey and the third edition of the American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia (undergoing copyediting version published in 2019) were included in the review. Guidelines included in the review were listed in a chronological order in Table 1. The review also included published expert opinions as well as consensus reports in addition to these guidelines.

Treatment of the Acute Phase

Main Principles

Before Starting the Treatment

Before starting the antipsychotic treatment, a physical examination including neurological examination should be performed. Body mass index, waist circumference, arterial blood pressure, heart rate should be measured, and the extrapyramidal symptoms should be checked. Those findings acquired by the aforementioned examinations are important for choosing the medication. Laboratory examinations should also be performed including full blood count, electrolytes, fasting blood glucose, lipid profile, liver, kidney and thyroid function tests as well as an ECG (especially the measurement of the QT interval). In case of an emergency, antipsychotics except clozapine may be started before results of the laboratory tests can be acquired (6).

Traditionally, antipsychotics have been classified into first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs). However, the validity of this type of classification has been questioned for the last years. Instead, the classification of each medication by their particular pharmacological mechanisms has been rising recently (7). From this point of view, antipsychotics can be classified as D2 antagonists, serotonin dopamine antagonists and the dopamine stabilizing agents.

Although antipsychotic polypharmacy is common in clinical practice (8), the evidence-base for their efficacy is low (9–11). The Schizophrenia

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Table 1. Guidelines included in the review

Guideline	Date
RANZCP (Royal Australian and New Zealand College of Psychiatrists), Clinical Practice Guidelines for the Treatment of Schizophrenia and Related Disorders.	2005
Canadian Psychiatric Association, Clinical Practice Guidelines. Treatment of Schizophrenia.	2005
PORT (the Schizophrenia Patient Outcomes Research Team) Psychopharmacological Treatment Recommendations	2009
Catalan Agency for Health Technology Assessment and Research, the Clinical Practice Guideline for Schizophrenia and Incipient Psychotic Disorder	2009
Psychiatric Association of Turkey, the Schizophrenia Treatment Guideline	2010
Singapore Ministry of Health, Clinical Practice Guidelines: Schizophrenia	2011
British Association for Psychopharmacology, Evidence-based guidelines for the pharmacological treatment of schizophrenia	2011
Harvard South Shore Program, the Psychopharmacology Algorithm Project	2013
SIGN (Scottish Intercollegiate Guidelines Network) Management of Schizophrenia	2013
NICE (National Institute for Health and Clinical Excellence) Psychosis and Schizophrenia in Adults: Prevention and Management.	2014
The Danish Health and Medicines Authority, Treatment of Adult Patients with Schizophrenia and Complex Mental Health Needs–A National Clinical Guideline	2015
World Federation of Societies of Biological Psychiatry, Guidelines for Biological Treatment of Schizophrenia	2009, 2012 (updated version), 2017 (short version)
Canadian Guidelines for the Pharmacological Treatment of Schizophrenia Spectrum and Other Psychotic Disorders in Children and Youth	2017
Canadian Guidelines for the Pharmacotherapy of Schizophrenia in Adults	2017
RAISE (the Recovery After an Initial Schizophrenia Episode) Project	2018
Polish Psychiatric Association, Recommendations for the Treatment of Schizophrenia with Negative Symptoms.	2019
The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia	2004, 2019 (undergoing copyediting version)

Treatment Guideline of Psychiatric Association of Turkey, in line with several other guidelines, recommends monotherapy with antipsychotics. The guideline highlights the importance of limiting antipsychotic polypharmacy to treatment resistance or temporary practices in case of mandatory situations (12).

Treatment in Particular Patient Groups

In 70% of schizophrenia patients, positive symptoms can be alleviated to a tolerable level (13). The effect sizes between antipsychotics (except clozapine) by their efficacy on acute positive symptoms are small. Furthermore, the superiority of antipsychotics on each other along this phase has not been consistently shown (7, 14). The treatment success of antipsychotics on negative symptoms is lower than positive symptoms. Recent results suggest that the disability related to negative symptoms may be alleviated via urgent interventions using new generation medications (15). However, any medication which can be claimed as effective to negative symptoms does not exist yet (16, 17).

Randomized clinical trials showed that clozapine might lower the risk of suicide attempts in patients with schizophrenia who were at high risk for suicide (18). Clozapine should be a treatment choice for these patients. Furthermore, American Psychiatric Association recommends switching to clozapine in patients whose aggression risk is still significant despite the use of other antipsychotics (14).

In case of psychomotor agitation, differential diagnosing should be carefully made, and the treatment should target the underlying cause. For example, akathisia may be missed in a patient who has problems describing the situation. Lorazepam was reported to be a favourable choice for psychomotor agitation due to akathisia (19). Furthermore, intoxication with psychostimulants or withdrawal of alcohol or benzodiazepine may lead to psychomotor agitation (20). If psychomotor agitation is caused by particular psychotic symptoms (e.g. commanding or directing voices or fear related to paranoia), antipsychotics or antipsychotic-benzodiazepine combinations can be used for the treatment (21). The Schizophrenia Treatment Guideline of Psychiatric Association of Turkey recommends intramuscular injections in case patients do not comply with oral treatments at the beginning of the treatment, or when a psychomotor agitation should rapidly be calmed. For this aim, haloperidol is the most commonly used agent. Injections of 5–10 mgs can be repeated every a few hours when necessary. However, it is recommended not to exceed 40 mg of intramuscular haloperidol doses per day. Furthermore, olanzapine injections can also be used for this aim in 10 mgs of doses. Similarly, it is recommended not to exceed 20 mgs of intramuscular olanzapine doses per day (12). Intramuscular zuclopenthixol acetate (*acuphase*) can also be used every 24–72 hours. As having a long activity period, it can be preferred in severe cases. The total dose of zuclopenthixol acetate should not exceed 400 mg, and more than 4 injections should not be made within 2 weeks. If a treatment for a period longer than 2 weeks is necessary, treatment can be switched to the decanoate form or the oral form. Despite the common clinical practice, guidelines do not recommend giving an intramuscular anticholinergic medication in combination with the zuclopenthixol acetate injection. On the contrary, this intervention was associated with increased risk of side effects (22). In order to decide a chlorpromazine injection, the risk of some important side effects such as severe postural hypotension, arrhythmia or lowering of epilepsy threshold should be considered, and chlorpromazine injections should be avoided as much as possible (22).

Treatment of First Episode Psychosis

Before Starting the Treatment

First episode psychosis is a period at which patients have higher chance to benefit from treatments. Furthermore, interventions on this period have significant effects on treatment adherence in the future. Careful differential diagnosing is crucial before starting the treatment. Mood disorders with psychotic features and psychotic disorders due to general medical conditions/substance use should be kept in mind among the differential diagnoses (12).

Which Medication?

First episode psychosis patients are highly vulnerable to the extrapyramidal side effects of antipsychotics. These plausible side effects may lead to increased anxiety of the patients as well as their relatives, and may lead to disrupted treatment adherence. Furthermore, extrapyramidal side effects have been associated with secondary negative symptoms, cognitive impairments, akathisia, poor prognosis and depression. Therefore, extrapyramidal side effects should be evaluated carefully, and antipsychotics with a relatively low risk of extrapyramidal side effects should be prioritized (14). On the other and, first episode psychosis patients are highly vulnerable to the metabolic side effects (23). The Schizophrenia Treatment Guideline of Psychiatric Association of Turkey recommends prioritizing SGAs rather than FGAs in first episode psychosis patients. FGAs are recommended in patients with a parenteral treatment need and with excessive/violent behaviour (12). Similarly, several guidelines as well as consensus reports recommends prioritizing SGAs in this phase (24–31). However, one guideline posits that FGAs and SGAs have no difference in terms of efficacy, and have different but equally important side effects in first episode psychosis patients (32). More recent guidelines do not prioritize any group of antipsychotics. These guidelines highlight the importance of joint decision making with the patients and their relatives (14, 33–38). An important proportion of recent guidelines recommend starting with an antipsychotic apart from olanzapine or clozapine (39). As a result, it seems to be appropriate starting the treatment with a SGA apart from olanzapine or clozapine.

Which Dose?

First episode psychosis patients may benefit from lower doses of antipsychotics in comparison with the patients in chronic phase (14). Generally, guidelines recommend the lowest dose which is both effective and causing no side effects. PORT (the Schizophrenia Patient Outcomes Research Team) recommends the lower half of the recommended dose range of all antipsychotics except quetiapine. For example, risperidone was recommended at the dose range of 1 to 3 mgs, and aripiprazole at 10 mgs. For quetiapine, the guideline states that the daily dose might need to be titrated to 500–600 mgs (39). Dose recommendations in the Schizophrenia Treatment Guideline of Psychiatric Association of Turkey, which are similar to the former guidelines, are presented in Table 2 (12). Three guidelines recommend antipsychotic use in 300–1000 mgs of chlorpromazine equivalent doses (24, 35, 40), two guidelines recommend 300–500 mgs of chlorpromazine equivalent doses (32, 39), and one guideline recommend lower doses (75–300 mgs of chlorpromazine equivalent doses) for first episode psychosis (25).

When to Change the Medication?

Three quarters of patients with acute schizophrenia respond to treatment within three weeks. It is stated that if the symptom severity does not decrease by one-quarter within two weeks, the possibility of achieving treatment goals within the next two weeks is not so high. Therefore, for outpatients, the Schizophrenia Treatment Guideline of Psychiatric Association of Turkey recommends waiting for three weeks following the titration to target doses. For inpatients, this guideline recommends switching to another antipsychotic in case there is no response at the end of the second week (12). Several guidelines and consensus reports, in line with the former guideline, recommend that the waiting period for one month is sufficient (29, 33, 34). Some guidelines state that a waiting period for two weeks is even sufficient (38, 41). However, some other guidelines recommend longer waiting periods such as 4 to 6 weeks (30, 32, 35, 37). In case of partial response, guidelines have recommended 4–12 weeks of waiting periods before switching to another antipsychotic (28, 29). As a result, 2 weeks of a waiting period in average may provide sufficient clues to predict a treatment response. However, one of the most important issues is how to assess 'response' . Considering patients' positive symptoms, lifestyle, self-care and characteristics of the relationships with his/her environment, approximately 25% or more improvement compared to the beginning of the treatment may help to decide whether the medication used would be beneficial. This decision may be made using reduction rates in Positive and Negative Syndrome Scale (PANSS) or the Brief Psychiatric Rating Scale (BPRS) scores.

Other Interventions and Electroconvulsive Therapy (ECT)

First episode psychosis is a period during which issues commonly emerge on acceptance of the illness by the patients' and their relatives, and on treatment collaboration. Providing a detailed psychoeducation to the patients and their relatives is certainly necessary for the success of pharmacotherapy. Involving family members in the treatment process, interventions to stop alcohol-substance use, developing the patients' social relationships and ensuring that they take part in working life as soon as possible have great contributions to the success of the treatment (42). The Schizophrenia Treatment Guideline of Psychiatric Association

Table 2. Dose recommendations for antipsychotic starting doses in the Schizophrenia Treatment Guideline of Psychiatric Association of Turkey

		Starting dose		
	Dose range	**With no medical history**	**First episode psychosis**	**Elderly**
Amisulpiride	200–1200 mg	200 mg	200 mg	200 mg
Aripiprazole	15–30 mg	15 mg	10 mg	10 mg
Haloperidol	5–20 mg	10 mg	5 mg	2 mg
Quetiapine	300–900 mg	50 mg	50 mg	25 mg
Clozapine	300–900 mg	12.5 mg	12.5 mg	12.5 mg
Olanzapine	10–30 mg	15 mg	10 mg	5 mg
Paliperidone	3–12 mg	6 mg	3 mg	3 mg
Risperidone	2–8 mg	2 mg	1 mg	0.5 mg
Sertindole	4–20 mg	4 mg	4 mg	4 mg
Zuclopenthixol	25–150 mg	25 mg	10 mg	10 mg

of Turkey states that ECT use in first episode psychosis should be limited to catatonia and to the risk of self-harm/harming others. The rationale behind is stated as the plausibly negative effect on treatment adherence as well as the insufficient evidence for the efficacy of ECT in this period (12).

Treatment of Acute Relapses in Individuals with a Previous Diagnosis of Schizophrenia

Before Starting the Treatment

World Federation of Societies of Biological Psychiatry states the key goals of treatment for acute psychotic relapses as follows: (i) The severity of the relapse should be alleviated as soon as possible in order to prevent a possible harm to the patient and their relatives (ii) The functioning of the patient should be regained as soon as possible (43).

Before starting the treatment, causes underlying the acute relapse should be investigated. Possible factors such as non-adherence to medication, substance use, severe psychological stress, organic aetiology etc. should be elaborated. If the medication is discontinued, it should be assessed whether this decision was made by the patient only or in collaboration with the physician. The reasons of the non-adherence should be enlightened (12). Some guidelines and consensus reports recommend using long acting injection forms of antipsychotics in case of non-adherence (28, 40).

Which Medication?

Unlike the recommendations for the treatment of first episode psychosis, the Schizophrenia Treatment Guideline of Psychiatric Association of Turkey does not prioritize FGAs or SGAs for the treatment of patients with a previous diagnosis of schizophrenia (12). However, several guidelines and consensus reports recommend SGAs as a first choice (24, 25, 31, 32, 41, 44). Patient's risk factors for possible side effects, medical history, previous antipsychotics used and the responses to those medications, preference of the patients as well as their relatives should be taken into account on the choice of the medication (14, 33, 36, 37, 45).

How to Follow-up the Patients?

If the acute relapse emerges while patients are (even partially) on medication, the Schizophrenia Treatment Guideline of Psychiatric Association of Turkey recommends increasing the dose through the highest end of the range. Furthermore, in case of the risk of self-harm or harming others, rapid intramuscular injections are recommended. If any single sign does not exist pointing out the alleviation of the acute relapse after treatment for one week, switching to another antipsychotic, primarily to another SGA should be considered. While switching to another antipsychotic, the receptor properties of the former antipsychotic should be taken into account. During the switching period, the dose of the former antipsychotic should be tapered after a maintenance period of 2 to 4 weeks at the same dose.

If an acute relapse emerges after a discontinuation of an antipsychotic, a stepwise approach is recommended by the Schizophrenia Treatment Guideline of Psychiatric Association of Turkey.

The first step is to use the discontinued antipsychotic for 2–3 three weeks. If a partial response is achieved, it is recommended to wait for 2–3 more weeks. If side effects such as extrapyramidal symptoms or sedation emerge, it is recommended to lower the dose through the lowest end of the range. An anticholinergic agent may be added in case extrapyramidal symptoms are not relieved following the lowering of the dose. If extrapyramidal side effects which have a significant negative effect on patients' quality of life or amenorrhea/galactorrhea emerge, switching to an appropriate SGA is recommended (12, 14).

As a second step, it is recommended to increase the dose of the antipsychotic used in the first step, and wait for 2 more weeks. If a response cannot be achieved despite a 4 weeks high dose antipsychotic use, switching the antipsychotic is advised. Recommendations in several other guidelines for the waiting period prior to switching the antipsychotic are similar (24, 38, 41). Furthermore, it is stated that the new antipsychotic should be from a different subgroup. Finally at this stage, clozapine may be a treatment option for appropriate patients (12).

Antipsychotics used in the first two steps should be taken into account on the selection of the antipsychotics at the third step. The Schizophrenia Treatment Guideline of Psychiatric Association of Turkey recommends a SGA if the antipsychotics used in the first two steps are FGAs. If the antipsychotics used in the first two steps are SGAs; it is recommended to use a SGA from a different subgroup or a FGA. Clozapine is specified as a strong option at this stage (12).

Treatment in Maintenance Phase

Before Starting the Treatment

World Federation of Societies of Biological Psychiatry and American Psychiatric Association state the key goals of treatment in maintenance phase of schizophrenia as follows: Maintaining the remission, improving the patients' quality of life and preventing possible relapses (14, 43). The Schizophrenia Treatment Guideline of Psychiatric Association of Turkey lists the key treatment goals at this stage under the following four subheadings: (i) Eliminating the symptoms of the illness (ii) Eliminating the side effects of the treatment (iii) Reducing the burden of the illness on the individual, family and the society (iv) Improving the patients' quality of life (46).

The Concepts of Remission and Recovery

The concepts of remission and recovery should be considered while planning the maintenance treatment of schizophrenia. Remission has been defined as having 'mild' or less severe points in the following eight items of PANSS, BPRS or Scale for the Assessment of Positive-Negative Symptoms (SANS, SAPS) for six months: Delusions, unusual thought content, hallucinations, disorganised thinking, mannerisms and posturing, blunted affect, passive/apathetic social withdrawal, lack of spontaneity and flow of conversation (47). This criterion includes assessments of the psychotic symptoms as well as the functioning (48).

Recovery has been defined as follows by Liebermann et al. (49): Symptomatic remission (ratings of 4 or less points for the positive and negative symptoms in BPRS for the following two years), well occupational functioning, being able to live independently and to establish close relationships. Although there are no complete consensus statements on the concepts of remission and recovery, the majority of current definitions include social-occupational functioning and well interpersonal relationships besides symptomatic remission (50).

The Follow-up Process

The Schizophrenia Treatment Guideline of Psychiatric Association of Turkey recommends scheduling follow-up visits every four weeks with patients compliant with the treatment, every 2–4 weeks with patients using a long acting antipsychotic, every week with patients in the initial 16 weeks of the clozapine treatment followed by every four weeks, and every day in case of stressful events when necessary. In those visits, negative symptoms, anxiety-mood symptoms and cognitive symptoms should be evaluated besides the positive symptoms. The flowchart of the guideline includes adding antidepressants in case of post-psychotic depression and appropriate treatment in case of substance abuse. Rapid realignment of the patients in social, educational and occupational areas is of great importance in this phase (14, 42, 46).

The Schizophrenia Treatment Guideline of Psychiatric Association of Turkey recommends evaluating possible side effects as a first manner in case of non-adherence to treatment during the maintenance phase. Side effects such as loss of energy and motivation, feeling dizzy, hypersomnia, stiff muscles and trembling, feelings of restlessness, having difficulty to sit and the need to move, blurred vision, dry mouth and sialorrhea, problems in memory and concentration, constipation, weight gain, sexual problems, menstruation problems, feelings of breast fullness, inability to fall or stay asleep may impact on patients' quality of life, functioning and adaptation capacity. If the side effect associated with the non-adherence is resistant akathisia or parkinsonism, dose of the antipsychotic should be lowered in a first manner. If the problems cannot be relieved in this wise, it is recommended to switch to a SGA. In case of tardive dyskinesia, it is recommended to switch to clozapine. In case of other side effects, switching to another SGA is recommended following a benefit-harm analysis (46). In case of moderate to severe tardive dyskinesia, the recently released version of the American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia recommends using reversible Vesicular Monoamine Transporter 2 (VMAT2) inhibitors (deutetrabenazine, tetrabenazine, valbenazine) as a first option, which is a different recommendation from the older versions (14). Although these agents are not on market in Turkey, deutetrabenazine and tetrabenazine are included in Turkish Pharmacists' Association's list of active medications available from abroad (51).

Which Medication?

For the maintenance phase, the Schizophrenia Treatment Guideline of Psychiatric Association of Turkey recommends using the agent which alleviated the acute symptoms and was well-tolerated by the patient. Although the guideline does not prioritize SGAs or FGAs in this phase, the opinion prioritizing SGAs is widely accepted (27, 41, 43, 52). Some guidelines recommend choosing the medication considering the previous effectiveness, side effects, compliance, physical illnesses of the patients and the long term treatment plan (14, 33, 34). One guideline recommends amisulpride, risperidone or olanzapine as a first choice for maintenance treatment, and marks chlorpromazine and the other low potency FGAs as alternative options (41). Furthermore, there are some guidelines prioritizing long acting antipsychotics for the maintenance treatment (34, 37, 43). Long acting antipsychotics are placed in the stage that patients do not accept oral treatment in a certain manner in the flowchart of the maintenance treatment in the Schizophrenia Treatment Guideline of Psychiatric Association of Turkey (46). Long acting antipsychotics should be used as a first option in patients with no insight and treatment collaboration, having coexisting substance use, and a risk of aggression or suicide. Long acting forms of the antipsychotics have some advantages such as better compliance, more stable plasma concentrations, and stronger connections with the treatment centre. The disadvantages are plausible difficulties to cope with some unexpected side effects such as tardive dyskinesia or neuroleptic malignant syndrome, and the probable anxiety felt by the patients that they have lost their independence. However, involving patients in the treatment process by sharing the possible treatment methods, options and their characteristics may be of great importance for managing these plausible problems as well as symptom relief and recovery.

Which Dose?

For the maintenance phase, the Schizophrenia Treatment Guideline of Psychiatric Association of Turkey recommends an interrupted use of antipsychotics at the possible lowest dose. It has been stated that this dose is generally 5–15 mg haloperidol equivalent doses (46). The other guidelines recommend 200–600 mgs of chlorpromazine equivalent doses (24, 38, 39, 41, 43, 52). One recent guideline recommends 4–6 mgs of risperidone equivalent doses (38). These doses are in line with the recommendation of the Schizophrenia Treatment Guideline of Psychiatric Association of Turkey. Furthermore, the guideline recommends 6.25–25 mgs of fluphenazine decanoate equivalent doses for long acting antipsychotics (46).

How long?

The Schizophrenia Treatment Guideline of Psychiatric Association of Turkey, in line with several guidelines and consensus reports, recommends 1 to 2 years of maintenance treatment following a first episode psychosis (24, 25, 31, 33, 34, 36–38, 43, 46). However, guidelines are less consistent in the recommendations for patients with multiple psychotic episodes. The Schizophrenia Treatment Guideline of Psychiatric Association of Turkey as well as the other contemporary guidelines recommend at least 5 years of maintenance treatment for patients with multiple episodes (24, 34, 46). However, one more recent guideline recommends a shorter (2–5 years) maintenance treatment (37, 38, 43). Finally, the Schizophrenia Treatment Guideline of Psychiatric Association of Turkey and World Federation of Societies of Biological Psychiatry recommend lifelong treatment for patients with frequent episodes of psychotic exacerbations, a history of dangerous behaviour and serious suicide attempts (46, 52).

A recent meta-analysis compares the outcomes of the patients who has continued their antipsychotic treatment for 7–12 months following the remission of a psychotic episode and who has discontinued and used a placebo. The results showed that patients who have continued their antipsychotic treatment have a significantly lower risk of relapse and a higher quality of life (53). However, evidence is limited for the maintenance treatment after the first year following the episode. In a randomised controlled study including patients who continued their antipsychotic treatment for 2 years following the first episode psychosis, dose of the antipsychotic was reduced in a group of patients, and the dose was maintained in the other group. More often relapses were observed in the group with the dose reduction compared to the group whose dose was maintained (54). On the other hand, 7 years follow-up of this sample showed interesting results. The rate of recovery was higher in the group with dose reduction considering the functioning of patients besides symptomatic remission (55). This result suggests that a subgroup of patients with schizophrenia may have favourable functioning with reduction of the doses of antipsychotics. However, evidence to predict this subgroup is insufficient (56). For the maintenance phase, physicians should consider the risk of psychotic exacerbations on the one hand, and side effects as well as plausible structural changes of the brain caused by long term antipsychotic use on the other (57). The Schizophrenia Treatment Guideline of Psychiatric Association of Turkey recommends that dose reduction in the maintenance phase should be considered only in patients with no positive symptoms. It is stated that the dose can be reduced by 20% each time, and at six months or one year intervals depending on the patients' conditions. Furthermore, in case the patient gets worse following the dose reduction, immediate return to the former dose is recommended (46). These recommendations seem to be rationale until the emergence of more robust evidence on this topic.

The duration of the maintenance treatment for first episode schizophrenia is a controversial issue. Studies assessing this topic have significant limitations. Experts have cautions for the sufficiency of a 2 years' maintenance treatment for these patients, and recommend extending the duration as long as possible. Furthermore, the decision to discontinue medication should not be merely made by considering the remission of psychotic symptoms only. Besides, lifestyle and occupational functioning of the patients are highly important. In patients whose psychosocial functioning does not improve, discontinuation of medications may lead to relapses.

CONCLUSION

Our knowledge on acute and maintenance treatment of schizophrenia improve day by day. However, many unanswered questions still remain on this topic. Therefore, the most valid management of schizophrenia is still the patient-based approach.

Considering the efficacy, no convincing and consistent evidence exists demonstrating the superiority of antipsychotics on each other except clozapine. Antipsychotic choice on acute phases should be made considering the long-term treatment plan and the possible side effects with a patient-based approach. Some guidelines state that olanzapine should not be used as a first option in first episode psychosis due to its metabolic side effects.

A wide consensus exists on a 1-2-year maintenance treatment with antipsychotics following the acute phase. However, expert opinion questions the sufficiency of 2 years for these patients. The decision whether to continue or to discontinue antipsychotics following the two years should be based on the risk of psychotic exacerbations, side effects of the antipsychotics, and the needs of each individual patient. However, while deciding to discontinue medication, physicians should be meticulous. The mere consideration that psychotic symptoms are on remission is not sufficient for the decision of discontinuation. It is absolutely necessary that the occupational and social functioning of the patient has improved.

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