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Polish Psychiatric Association diagnostic and therapeutic management guidelines for patients with early-onset schizophrenia

Małgorzata Janas-Kozik[1], Dominka Dudek[2], Janusz Heitzman[3], Barbara Remberk[4], Jerzy Samochowiec[5], Agnieszka Słopień[6], Adam Wichniak[7]

[1] Paediatric Centre in Sosnowiec, Clinical Department of Psychiatry and Psychotherapy of Developmental Age, Medical University of Silesia in Katowice

[2] Department of Adult Psychiatry, Chair of Psychiatry, Jagiellonian University Medical College

[3] Department of Forensic Psychiatry, Institute of Psychiatry and Neurology in Warsaw

[4] Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Neurology in Warsaw

[5] Chair and Department of Psychiatry, Pomeranian Medical University in Szczecin

[6] Department of Child and Adolescent Psychiatry, Poznan University of Medical Sciences

[7] Third Department of Psychiatry, Institute of Psychiatry and Neurology in Warsaw

Summary

Early onset of schizophrenia (before the age of 18 years) is associated with a higher risk of delayed or missed diagnosis, more severe course of the disease, and an increased susceptibility to adverse reactions to antipsychotic drugs. The objective of this paper is to present the recommendations for the diagnostic and therapeutic management of patients with early-onset schizophrenia, developed on the basis of a literature review and a consensus of a group of experts working with schizophrenia therapy.

The formal criteria that must be met to diagnose schizophrenia are the same for children and adults. Early-onset schizophrenia must be thoroughly differentiated from uni – or bipolar affective disorder, autism-spectrum disorders (ASDs) and anxiety disorder. Diagnostic assessment for psychotic disorders is also necessary in the case of abnormal, destructive or aggressive behaviour, or self-harm.

The mainstay of schizophrenia treatment is pharmacological therapy, which is used in the treatment of acute episodes and in maintenance treatment – prevention of relapses. However, the use of pharmacological interventions in children and adolescents only to reduce the risk of psychosis development is not justified. Antipsychotic agents significantly differ by their

tolerance profile and clinical efficacy. Second-generation antipsychotic agents approved for the treatment of early-onset schizophrenia – aripiprazole, lurasidone and paliperidone – enable its effective and safe treatment. The necessary complement to pharmacological therapy is non-pharmacological interventions that should be adapted to the patient's age, cognitive abilities, disease stage and the needs of the whole family.

Key words: early-onset schizophrenia, guidelines, treatment

Introduction

In 12–35% of the patients, the first symptoms of schizophrenia appear before the age of 20; in 4% of them the onset occurs before the age of 15, and in 1% – before the age of 10 [1]. Early-onset schizophrenia not only represents a diagnostic challenge but may also entail considerable difficulties in terms of treatment. In comparison with schizophrenia that has its onset in the later period of life, early and very early onset psychosis is associated with a more severe psychopathology [2]. Untreated schizophrenia-spectrum disorders in children and adolescents are associated with a risk of concomitant diseases, substance abuse and physical health issues [3]. The risk of dangerous behaviour in schizophrenia is higher in persons with an earlier onset of the disease [4]. Moreover, earlier onset of psychosis is a predictor of a potentially worse prognosis, and about 30% of patients require long-term intensive social, emotional and psychiatric support [5]. The objective of this paper is to present the recommendations for the diagnostic and therapeutic management of patients with early-onset schizophrenia, developed on the basis of a literature review and a consensus of a group of experts working with schizophrenia therapy.

Early-onset schizophrenia – definition and prodromal, axial and additional symptoms

Early-onset schizophrenia manifests itself in the early period of development in children and adolescents before the age of 18, and very early-onset schizophrenia manifests itself before the age of 13. The prevalence of the disease in children under 13 years is low and amounts to 0.04% [6]. However, its incidence increases sharply after the age of 14 years, especially in boys – it is responsible for about 25% of all psychiatric hospitalisations in paediatric patients between the ages of 10 and 18 [1]. Early onset of schizophrenia is more common in boys. In the childhood period this predominance is clear, and in the adolescence period it gradually decreases with time.

The formal criteria that must be met to make the diagnosis are the same for children and adults. The clinical presentation of schizophrenia with an onset in the late adolescent period often resembles the disease in adults. However, the younger the child, the more visible the differences in the course of the disease.

The symptomatic spectrum of early-onset schizophrenia includes disturbances of thinking (delusions, hallucinations), emotions and behaviour. This form of the disease has also been associated with a greater severity of cognitive dysfunction in comparison with adults [7]. Each of these areas of mental activity may have a profound impact on

the psychological and social development. Although in the recent years prognosis data have become more optimistic than in the previous decades, early-onset schizophrenia is still considered a disease with a risk of a negative course. Therefore, the earlier the diagnosis and treatment initiation, the higher the chances for positive effects of therapy.

The onset tends to be slower and more insidious in younger patient groups, with more pronounced withdrawal and negative symptoms. Worsened functioning, social isolation or behavioural changes are non-specific symptoms that need to be thoroughly assessed while taking into account schizophrenia in the differential diagnosis.

Symptoms that are often the first to be noticed by the patient's environment are difficult behaviours that are often considered oppositional but are a result of misperception of reality. Unfortunately, pre-existing abnormal thoughts or hallucinations are often diagnosed only later – during a psychiatric examination. Disorganised speech may also be one of the positive symptoms of schizophrenia. It is easier to attribute colloquially understood behavioural disorders, fantasising, illogical and inadequate speech of a child to childish defiance and individualism in mental development rather than to a serious psychiatric disease. Vigilance is always necessary when the child's school performance suddenly begins to worsen, in a temporary relationship with bizarre behaviours and statements. It should be reason for concern for the caregivers and physician if the child changes his or her hygiene or dressing routines, and begins to distance him/herself from the family and peers. Disturbing signals are sudden outbursts of aggression and agitation. A noticeable change in expression of emotions may be observed in the child. Other potential symptoms include unjustifiably depressed mood, irritability, anxiety states and subsequently suspiciousness and distrustfulness towards family members or schoolmates and school staff. In younger children, the characteristic symptoms of early-onset schizophrenia commonly include such symptoms as confusing dreams or TV shows with reality. Although the lack of criticism is generally a symptom of schizophrenia, children may be completely unaware that their experiences differ from what others are experiencing ('I thought everyone heard voices'). In contrast, adolescents' complaints about bad relations with parents or bullying at school require a thorough analysis to determine which events took place in reality and which statements may suggest positive symptoms. Running away from home or alcohol, drug or nicotine abuse can also be – among many other symptoms – the first symptom of the developing disease. Self-harm is also a relatively common phenomenon in the adolescent population. Nevertheless, self-harm that is serious, bizarre, unusual in form or unusually explained should attract the attention of the clinician.

A serious danger associated with early-onset psychosis is also suicidal ideation, intentions and acts [8, 9].

Diagnostic assessment of the first psychotic episode in children and adolescents

The first psychotic episode may be preceded by a prodromal period in which the appearing symptoms usually take a non-specific form. The possible affective disorders are depression, anxiety, emotional lability and irritability. As regards thought disorders

or cognitive disorders, the patient can report bizarre and unusual ideas, and worsened functioning at school and in the peer group is observed. There is often a change in the sense of self or environment. On the other hand, the dominant behavioural problems are social withdrawal, loss of interests, suspiciousness, and deterioration in playing social roles. Physical symptoms appear in the form of sleep and appetite disturbances, loss of energy and decreased motivation.

In a large proportion of cases, the first episode of schizophrenia in the adolescent period has a typical presentation. The most common differences are in non-specific general symptoms. The differences in cognitive and linguistic development have an impact on the scope and quality of psychotic symptoms. In the case of children, systematised delusions and catatonic symptoms are less common, while hypochondriacal delusions and dysmorphophobias are more common. Patients in this age group more frequently experience auditory hallucinations (voices of monsters, toys, animals) and also those in other modalities, particularly the visual, tactile, olfactory and somatic sensations. The observed compulsions are most often egosyntonic. Moreover, suicide attempts that are difficult to explain (without affective symptoms or with a lack of coherent psychological motivation) may occur.

What are the symptoms in atypical forms? The pseudopsychopathic presentation is dominated by isolation, refusal to go to school, and active and verbal aggression. The pseudoneurotic presentation is characterised by the presence of attention deficit, worse performance at school, somatic and hypochondriacal complaints, and fears. In the obsessive-compulsive presentation, compulsions, self-harm and depressed mood predominate. As to the emotions, anxiety and its severity are important predictors of threatening behaviours.

During the first episode of schizophrenia, positive symptoms are fairly easy to diagnose, and thus it is easy to pose the right diagnosis and initiate the appropriate treatment. On the other hand, negative symptoms can often suggest depressive mood disorders, behavioural disorders in their colloquial understanding or other behavioural disorders that are difficult to explain.

Psychiatrists are often asked how to distinguish disease symptoms from broadly understood adolescent rebellion. In fact, normative crisis differs from the pathological one in that the greater the number of areas of the teenager's life that get out of their control – i.e. when it is difficult for them to cope with the challenges at school, with peers or with family – the greater the likelihood that the normative crisis will transform into a pathological one. The associated difficulties may take the form of positive or negative disease symptoms, which always raise many doubts as to whether the young person is not "pathologised" [10, 11].

Differential diagnosis of early-onset schizophrenia

Early-onset schizophrenia must be thoroughly differentiated from uni – or bipolar affective disorder, autism-spectrum disorders (ASDs) and anxiety disorder. Diagnostic assessment for psychotic disorders is also necessary in the case of symptoms of abnormal, destructive or aggressive behaviour or self-harm.

The first manifestation of early-onset bipolar disorder (BD) is often mania with psychotic symptoms and elements of disorganised behaviours and thoughts. About 50% of the persons whose BD started from a manic episode at a young age are initially diagnosed with schizophrenia [12]. The dominance of irritability, hostility or aggressive behaviour in the course of mania is sometimes interpreted as schizophrenic behavioural disorders. A severe affective episode may be accompanied with catatonic symptoms, auditory hallucinations, mood-incongruent delusions, various bizarre ideas, formal thought disorders, and even incidentally primary Schneiderian symptoms, treated by many psychiatrists as hallmark features of schizophrenia. Depressive states, especially after such a polysymptomatic episode of mania, can be misinterpreted as negative symptoms [13]. Similar neurobiological changes underlie this variable clinical presentation and frequent similarity of the initial episodes of BD and schizophrenia. It has been evidenced that neuroanatomical changes in the volume of brain structures do not differ between people with BD and schizophrenia, at least in the first phases of the disease. The only differentiating finding is a greater reduction in the volume of white matter in people with the first episode of BD, and a greater reduction in the volume of grey matter as well as enlargement of the lateral ventricles in initial schizophrenia. In addition, many studies have found that both diseases share common genetic, electrophysiological and biochemical characteristics, which may be responsible for the overlap of their psychopathological symptoms [14].

The differential diagnosis should take into account the entire history of the disease (what any potential previous episodes looked like, how the symptoms changed over time, how the patient functioned in periods of improvement). An important clue may be family history (more frequent occurrence of affective disorders in the families of BD patients) and the efficacy of mood stabilisers. Premorbid functioning and prodromal features are also worth analysing. There are differences between the prodromal symptoms of BD (mania) and schizophrenia; the former is considerably more often associated with symptoms such as decreased concentration and attention, physical agitation, tiredness, lack of energy, depressive mood, difficulty in thinking and clear communication, mood lability, obsessions and compulsions, while unusual thoughts are more common prodromal symptoms of the latter [15].

In a meta-analysis conducted by Zeng et al. [16] that encompassed almost two million subjects, persons with ASD were found to be 3.55 times more likely to be additionally diagnosed with schizophrenia in comparison with the control group. ASD is a neurodevelopmental disorder in which the first symptoms appear in early childhood. In the case of schizophrenia, the patient's mental state changes later, usually in the adolescent period. As demonstrated by the completed studies, some negative symptoms, especially deficits in social communication and social-emotional reciprocity, may be shared by both these disease entities. In schizophrenia, negative symptoms include, for example, blunted or shallow affect, decreased use of gestures and eye contact in communication, speech impoverishment (possibly associated with formal thinking and cognitive disorders), avolition and apathy, and lack of social interest and attentiveness. On the other hand, deficits in non-verbal communication, limited use of gestures and eye contact when communicating with others as well as limited emotional sharing,

spontaneous communication and fluidity of conversation are among the symptoms described in ASD [17]. A different situation exists in the case of positive symptoms in ASD and schizophrenia, which are more characteristic of the individual entities and thus are much more useful for their differentiation [18]. Patients with schizophrenia exhibit hallucinations, delusions, bizarre behaviour, positive formal thought disorders (e.g. disorganised thinking, incoherent speech). Among the positive symptoms in ASD, researchers note abnormalities that appear in speech (e.g. echolalia, atypical intonation), atypical social behaviour (e.g. excessive, atypical gesticulation or facial expressions, inadequate social behaviour), stereotypical and repetitive behaviours, insistence on constancy, unusual sensory sensitivity, motor stereotypies or mannerisms, and limited interests.

States of fear and anxiety that occur in healthy children may be adequate to the level of development of the child and do not have to be interpreted as symptoms of a mental disorder. However, if anxiety accompanies psychotic symptoms associated with disorders of thought or perception, if it is inadequate and irrational, it can be treated initially as a prodromal symptom of schizophrenia, and as psychosis develops, as a strong emotional reaction to psychotic experiences.

A significant symptom in the presentation of early-onset schizophrenia may be anxiety that has to be differentiated from other anxiety disorders that are common in children. Anxiety disorders, which may be accompanied by behavioural disorders, aggression, dysphoria or irritability, can be too hastily classified as a schizophrenia-accompanying symptom if possible separation anxiety, specific phobia, generalised anxiety disorder, panic disorder, post-traumatic stress disorder or obsessive-compulsive disorder are not excluded [19, 20].

Aggressive behaviour causes physical threat or harm to other people or animals. These include bullying, threatening, intimidating others, frequent initiation of physical fights, use of weapons that may cause serious physical injury, physical cruelty to people and/or animals, theft directly from the victim (extortion, pickpocketing and other), knowingly participating in arson with the intention of causing serious harm, and knowingly destroying someone else's property. They can also be encountered in people with so-called positive symptoms, i.e. delusions, which are disorders of thought, and hallucinations, which are disorders of perception. Because of the disease, such people –who often behave incomprehensibly and bizarrely for us – may also exhibit aggressive behaviour. The disease can make it impossible for them to recognise the meaning of an aggressive act or to refrain from aggressive behaviour. Behavioural disorders are perpetuated antisocial, aggressive or rebellious behaviours. They cause violations of other people's rights and rules of social coexistence. These behaviours considerably exceed the norms for the given age and cultural environment. Their extreme forms are criminal behaviour and conflicts with the law. They are a non-specific risk factor for the development of almost all psychiatric disorders.

Due to the difficulties with identification and thus treatment initiation, early-onset schizophrenia can be a serious life-threatening condition for a child. A common complication of this psychosis, reaching 40% of the cases, is self-harm, which can lead to suicidal attempts and suicide when not taken seriously. The most common types

of self-harm include self-scratching, self-hitting, self-biting, self-pinching, violent and persistent head banging, and pulling out one's hair. Characteristically, children diagnosed with schizophrenia did not respond to their own injuries or self-inflicted pain, and sometimes even gave the impression of enjoying these behaviours. There are studies that indicate that self-harm in children and adolescents is associated with an increased risk of subsequent suicide not only until the age of 18 years, but also in adulthood. Self-harm sometimes contributes to the diagnosis of early-onset schizophrenia in children who have previously been given many different diagnoses and have not been effectively treated [19, 20].

Early intervention in the first psychotic episode in a juvenile patient

As it is known, schizophrenia treatment includes treatment of an acute episode (treatment of the first episode and exacerbation therapy), maintenance treatment and prevention of relapses. In the case of adults, the possibility of using (different) medicines and forms of psychotherapy if there is a risk of psychosis is also analysed. As to children and adolescents, in 2015 the recommendations of the European Psychiatric Association (EPA) expressed an unequivocal position that the use of interventions in children and adolescents aimed only at reducing the risk of developing psychosis is not justified [23]. Comprehensive care corresponding to the child's current needs and mental status monitoring with adequate modification of the treatment are necessary.

A more recent meta-analysis also makes no indications as to any method being effective in preventing the development of psychosis in children and adolescents [24]. Single controlled studies on the use of omega-3 acids, family therapy and cognitive remediation have yielded promising results. At baseline, most subjects of the analysed studies received some form of psychotherapy as well as psychotropic drugs. In particular, 30% of the study subjects received antipsychotic agents at baseline. Indications for which these medicines were used are not specified.

Another area of systemic interventions aimed at improving the prognosis is attempts to diagnose the disease and start treatment earlier and to shorten the period of untreated psychosis. The interventions used include screening and creation of specialised care centres. Screening for psychosis may be conducted in the general population (e.g. screening on school grounds is possible, although associated with many logistical difficulties and the need to consider ethical issues, as described by Meyer et al. [25]), or include only those persons who seek help. The care should be comprehensive and early intervention services are often addressed to adolescents and young adults. The authors of a review of early intervention programmes state in their conclusions that the efficacy of the analysed projects is promising – in particular it was associated with a reduced number of hospitalisations of patients participating in therapy [26]. Nevertheless, clinical interventions alone are not sufficient to shorten the period of untreated psychosis in the whole population; it is necessary to improve treatment access/demand. Means to achieve this objective include extensive educational campaigns.

Pharmacological treatment

Schizophrenia treatment includes treatment of the first episode, maintenance treatment, treatment of exacerbations and prevention of relapses. The use of antipsychotics is considered absolutely necessary (see the discussion about the period of untreated psychosis). It is also mandatory to use psychosocial interventions. According to the NICE and Canadian guidelines [1, 27], the diagnostic process should take into account the developmental history, physical and mental health, as well as psychological, family, social, economic and educational situation of the patient. In case of treatment failure, the investigation to find its causes should take into account such possibilities as patient non-compliance, somatic diseases, and the use of additional medicines or psychoactive substances. Patient care should be provided by a multidisciplinary team.

Although treatment is usually started with second-generation antipsychotics, there is no unequivocal recommendation to use them. Caution is advised in the case of olanzapine – the decision to initiate treatment with this medicine should be discussed in detail with the patient and parent in view of the clinically significant risk of development of metabolic complications. If two properly conducted treatments prove to be ineffective or are not tolerated, clozapine can be used after a thorough analysis of the possible causes of the lack of treatment effect. The use of this substance in children and adolescents is discussed in the professional literature [28]. In the absence of a therapeutic effect of clozapine, monitoring of its blood levels should be considered, and the patient's previous management, state of health and situation along with the possible causes leading to the persistence of symptoms should be re-analysed. Subsequently, treatment augmentation through adding a second antipsychotic agent may be considered. The recommendations do not explicitly mention electroconvulsive treatment as the next step, but experts consider this method of treatment to be valuable in selected situations and used too rarely in the group of children and adolescents [29]. The use of other neuromodulatory techniques is only experimental.

Many medicines used in the first-line treatment in adults are not approved for use in children and adolescents. Antipsychotic agents that are approved in Poland for use in patients with early-onset schizophrenia are listed in Table 1, and those approved for use in other indications are listed Table 2.

Table 1. **Medicines approved in Poland for the treatment of early-onset schizophrenia**

Medicine	Approved conditions of use
Amisulpride	Not recommended in patients under 18 years of age; contraindicated in patients under 15 years of age/prepubescent patients
Aripiprazole	From 15 years of age
Chlorpromazine	From 1 years of age (the labelling does not reflect the current medical knowledge)
Haloperidol	From 13 years of age, following the failure of other treatments
Clozapine	From 16 years of age
Levomepromazine	From 12 years of age

table continued on the next page

Lurasidone	From 13 years of age
Paliperidone	From 15 years of age (the medicine is practically unavailable in Poland in an oral form)
Perazine	From 16 years of age
Sulpiride	From 14 years of age

Table 2. **Antipsychotic agents approved in Poland for the treatment of early-onset psychiatric disorders**

Medicine	Approved conditions of use
Aripiprazole	From 13 years of age in manic episodes (lower age threshold than in the case of schizophrenia)
Haloperidol	From 10 years of age in tics (lower age threshold than in the case of schizophrenia)
Risperidone	From 5 years of age in behavioural disturbances/in the case of aggressive behaviour
Tiapride	From 6 years of age; therapeutic indications: dementia, behavioural disorders during alcohol withdrawal, severe form of Huntington's chorea (we do not expect these diseases in children; nevertheless, this is stated in the summary of product characteristics)
Ziprasidone	From 10 years of age, in mania and mixed episodes

As shown above, there are only few second-generation antipsychotic agents that are approved for use in children and adolescents, especially in the younger adolescents. The off-label use of the medicine requires the legal guardians and the patient to be informed in detail about the possible associated risks. The legal guardian and the patient above 16 years of age should provide a special consent for the medicine to be used.

In conclusion, a meta-analysis by Sarkar and Grover [30] showed that the current evidence for the use of antipsychotics in children and adolescents with schizophrenia is rather limited, although antipsychotics are regarded as effective in the treatment of schizophrenia also in this age group. Similar conclusions are drawn from the literature studies on the use of long-acting antipsychotics (LAI) in children and adolescents [31]. In another meta-analysis of atypical antipsychotics in schizophrenia in children and adolescents, lurasidone was associated with similar efficacy, lower body weight gain, and a lower risk of complete drug discontinuation compared to other atypical oral antipsychotics [32]. A slightly older meta-analysis showed that olanzapine was associated with the highest weight gain and aripiprazole with the lowest. For the secondary endpoint, although many active comparative studies had been identified, the data were not available for meta-analysis and were too limited to draw firm conclusions [33].

The issue of obesity in the juvenile and young adult population and metabolic symptoms as a consequence of treatment with neuroleptics

Obesity and metabolic disorders induced by antipsychotic treatment are both among the most common as well as clinically most relevant complications of pharmacologi-

cal treatment in schizophrenia. They increase the risk of not only diabetes, but also cardiovascular disease. For these reasons, the assessment of cardiometabolic risk prior to initiation of antipsychotic treatment, repeated after six weeks and three months of treatment and then not less frequently than once a year, is presently recommended as a constant element of schizophrenia treatment [34].

Although the risk of cardiometabolic disorders is strongly associated with an age above 40 years, this does not mean that in the treatment of early-onset schizophrenia less attention can be paid to the metabolic risk assessment parameters. On the contrary, the available data indicate that patients at a younger age are more susceptible to the metabolic adverse effects of antipsychotic agents than older people. For this reason, already when initiating pharmacological treatment of the first episode of schizophrenia, psychiatrists should be guided by the general treatment principles that reduce the risk of metabolic disorders. Selection of the antipsychotic drug should be guided not only by its effectiveness, but also by the risk of metabolic syndrome. Antipsychotic agents with the lowest risk of weight gain are ziprasidone, lurasidone, aripiprazole, haloperidol, brexpiprazole and cariprazine [34–36].

If a metabolic disorder is found, antipsychotic treatment should be modified by reducing the drug dose, augmenting the treatment with another antipsychotic agent with a low risk of weight gain, or switching the antipsychotic treatment to such a medicine. Appropriate somatic treatment (metformin, statins, etc.) should be used and in cases of alcohol abuse and smoking, patients should be motivated to change their lifestyle with effective behavioural and pharmacological interventions [34]. What is important, health promoting education alone is not sufficiently effective [36].

Antipsychotic treatment conducted in this way is safe and, on the basis of long-term records of the use of antipsychotic drugs, reduces the risk of premature death in people suffering from schizophrenia as well as the risk of premature death associated with cardiovascular diseases [37].

Effect of neuroleptics on cognitive functions

After the introduction of second-generation antipsychotic agents, a hope appeared that they may be effective against cognitive impairment in schizophrenia [38]. However, further analyses brought less consistent data and there is also a very limited number of placebo-controlled studies [39].

In early-onset schizophrenia, few open-label clinical trials indicated an improvement of cognitive function in the course of treatment [40–42]. None of the antipsychotic agents was found to be superior to any of the others in comparative trials [41, 43]. Although placebo-controlled clinical trials often take into account the cognitive component of schizophrenia dimensions, there are no publications that would present the treatment effect in juvenile patients.

Search is ongoing for pharmacological mechanisms that could increase the efficacy of antipsychotics and/or reduce their typical adverse effects, such as metabolic syndrome, QT prolongation on ECG, and cognitive and motor disorders. In the treatment of cognitive impairment, one of the targets is the 5-HT7 serotonin receptor, with

particular emphasis on the second-generation antipsychotic agent lurasidone recently registered in some countries [44].

The 5-HT7 serotonin receptors are present in the central and peripheral nervous system. In the brain, they are detected mainly in the frontal cortex, thalamus, hypothalamus and hippocampus [45]. The distribution of 5-HT7 receptors in the central nervous system indicates their role in regulation of cognitive processes, mood, pain, circadian rhythms and sleep [46]. Accordingly, both inactivation of the gene for the 5-HT7 receptor and pharmacological blockade of this receptor produced "antidepressant" effects in animal models of depression symptoms [46]. The distribution and physiological functions of 5-HT7 receptors have prompted several research groups to develop molecules with a high affinity for the 5-HT7 receptor, intended for the treatment of various neuropsychiatric disorders, including schizophrenia, cognitive impairment and depression.

Harvey et al. [47] evaluated the effects of lurasidone on cognitive function in adult patients with schizophrenia recruited to a six-week double-blind study and randomised to treatment with lurasidone (80–160 mg), quetiapine XR (200–600 mg) or placebo, respectively [47]. Cognitive performance was assessed with the CogState computerised cognitive battery. In the population of patients meeting the evaluation criteria, lurasidone 160 mg was superior to both placebo and quetiapine on the neurocognitive composite, while lurasidone 80 mg, quetiapine XR and placebo did not differ. Patients who met the predefined criteria entered a six-month double-blind extension study evaluating lurasidone (at a dose of 40–160 mg) in comparison with quetiapine XR (at a dose of 200–800 mg). In the extension study, analysis of the full sample demonstrated a significant better effect on cognitive performance in the group treated with lurasidone than in the group treated with quetiapine XR, both at three and at six months [47]. The results of the study conducted by Harvey et al. [47] confirm the concept of combining the unique pharmacological profile of lurasidone with a beneficial effect on cognitive deficits typical of schizophrenia.

Long-term improvement in insight and judgement, as well as schizophrenia symptom severity, was significantly greater for lurasidone 40 to 160 mg/d compared to quetiapine XR 200 to 800 mg/d assessed over a double-blind, six-month continuation treatment period that followed the six-week acute treatment study.

Cardiac safety

There are only very limited data on cardiac safety of antipsychotic agents from studies in groups of children and adolescents. In a study by Ray et al. [48] based on the analysis of Medicaid registers, the risk of death in children, adolescents and young adults (up to 24 years of age) receiving antipsychotics at a dose exceeding the equivalent of 50 mg of chlorpromazine was assessed as 3.5 times higher than in the group of youths using psychotropic agents of other classes. This study looked at deaths regardless of their cause and did not consider the individual drugs [48].

A meta-analysis analysing the effects of using nine antipsychotic agents, first – and second-generation ones, found that the use of aripiprazole was associated with

significant shortening of the QT interval on ECG while the use of ziprasidone was associated with its prolongation. QT prolongation from the baseline was also observed in the case of risperidone, but the difference from placebo did not reach statistical significance [49]. There are also no data that would unequivocally indicate to what extent QT prolongation described in the meta-analysis translates into the clinical risk for a paediatric patient. In a more recent study analysing a Taiwan population database, including 29,030 patients aged 5-18 years, no differences were found between the assessed medicines (amisulpride, aripiprazole, haloperidol, risperidone, olanzapine, paliperidone, quetiapine, sulpiride, ziprasidone) in the risk of hypertension and serious cardiovascular events [50].

Studies in adults show that in this age group antipsychotics differ significantly in terms of cardiac safety, including the risk of prolongation of the QT0 interval that can lead to ventricular arrhythmias of the torsade de pointes type. According to meta-analyses of the cardiac safety of antipsychotics in adults, the antipsychotic agents with the lowest risk of QT prolongation are lurasidone, brexpiprazole, cariprazine and aripiprazole [51].

An important complication that should be borne in mind during clozapine treatment is also myocarditis [28].

Other adverse effects of neuroleptic agents

The use of antipsychotic agents in the paediatric population may be associated with more common adverse effects in comparison with adults. Liu et al. [52] analysed the incidence of adverse effects in children and adolescents. They used study materials made available by FDA and results of studies that referred to drug approval documents. The number of paediatric patients participating in the studies ranged from 106 to 472. The assessed antipsychotic agents included aripiprazole, paliperidone, lurasidone 40 mg/d and 80 mg/d, risperidone, asenapine, quetiapine and olanzapine. In children and adolescents, a significantly higher risk of sedation (except lurasidone), extrapyramidal symptoms (risperidone) as well as fatigue and abdominal pain (risperidone) was observed in comparison with adults. For most of the analysed areas of action of aripiprazole, lurasidone and paliperidone, the risk of adverse effects was assessed as lower in comparison with adults. In the case of aripiprazole, it had a definitely favourable safety profile in terms of sleep disorders, anxiety, agitation and headaches.

In a meta-analysis conducted by Krause et al. [53], extrapyramidal symptoms were found to be more common with paliperidone versus placebo and with aripiprazole versus quetiapine. That analysis demonstrated a significantly more common appearance of extrapyramidal symptoms after the use of haloperidol, risperidone and quetiapine in comparison with placebo. Much higher sedation in comparison with placebo was observed after risperidone, aripiprazole, paliperidone, asenapine and clozapine. An increase in prolactin levels was also assessed – it was greater with risperidone and haloperidol and significantly lower with aripiprazole and asenapine.

In their publication, Ray et al [48]. presented disturbing results of the conducted studies. Based on registry data, they compared the risk of unexpected death among

58,497 patients aged 5-24 years taking antipsychotics and other psychotropic drugs (psychostimulants, antidepressants). Among those who received a dose greater than or equal to the equivalent of 50 mg of chlorpromazine, the hazard ratio for death was 3.5 in relation to the control group; this risk meant 45 excess deaths per 100,000 patient-years.

Non-pharmacological treatment used in the treatment of psychotic disorders in children and adolescents

Non-pharmacological (psychological) interventions also play an important role in the treatment of schizophrenia in children and adolescents. They should be adapted to the patient's age, cognitive abilities, disease stage and the needs of the whole family. Disease of a child is a difficult experience for the whole family constituting a threat to its normal functioning. Therefore, family interventions play an important role in improving the functioning of the patient and the patient's family as well as the course of the disease itself. Family therapy may be conducted with one family or in the form of multi-family therapy (MFT) in which several families are invited to participate [27]. It may begin during acute symptoms of the disease or later. Family therapy provides an opportunity to discuss the relations between individual family members and makes it possible to reduce excessive expression of emotions, and thus reduces the risk of relapse. One of the approaches recommended for individual work with the patient is cognitive-behavioural therapy (CBT) [27]. Treatment objectives are determined on a case-by-case basis. They may include, for example, learning to recognise relationships between thoughts, feelings and behaviour of the patient and the current or past symptoms and/or functioning, work on the acceptance of experiences, and also stress reduction. Similarly as in the case of pharmacological treatment, it is important to monitor the efficacy and safety of psychological interventions, and the psychotherapeutic process should be supervised.

To support patients with schizophrenia, art therapy is also recommended, especially to relieve negative symptoms. It is advisable to conduct it in a group of patients. Art therapy can be started during the acute phase of the disease and continued on an outpatient basis. It includes psychotherapeutic elements, enables patients to creatively express their own experiences, experience themselves and their symptoms differently, accept and understand the feelings that appeared during severe psychotic symptoms, and also creates possibilities of development of interpersonal relations [27].

Also believed to be effective in the treatment of patients with schizophrenia are cognitive remediation therapy (CRT), social skills training, group therapy, cognitive remediation (known as non-pharmacological methods of reducing cognitive deficits in schizophrenia) or cognitive function training, as well as physical activity [54, 55].

Psychoeducation of the patient and family and other psychosocial interventions (educational and vocational support, family interventions, participation in peer support groups)

Psychoeducation is one of the most important tasks in the therapy and prevention of psychosis relapse in patients who have been diagnosed with early-onset schizophrenia. The psychoeducation process includes a complex programme of family interventions conducted by the therapist, involving the child and parents (guardians). Within this process, provision of information about the disease should be accompanied by teaching the child and parents (guardians) how to cope with stress, solve problems and improve communication. The purpose of medical education is to protect the patient from potential life adversities and additional suffering. It should result in the acquisition of the ability to separate psychotic and non-psychotic sensations, gain insight into the disease, prevent stigma and self-exclusion from social life. Explanation of the nature of the disease, methods and duration of treatment or possible adverse effects must be provided in a simple, concise and understandable way. The objective of psychoeducation is to make the patient and family members accept the very fact of the disease, which is an extremely traumatic experience. This can take a long time and make it necessary to overcome a lot of resistance, including guilt and trying to blame each other for the disease. The paralysing fear of parents confronted with the diagnosis of the child's schizophrenia triggers the mechanisms of defence, denial and shifting responsibility to themselves. There may also be attempts to explain the cause of the disease in a completely irrational way. The basic elements of psychoeducation must be adapted to the child's age, development level and other disorders overlapping the symptoms of schizophrenia. In younger children these can be self-aggressive behaviours, specific phobias, intrusive and compulsive activities, and in adolescents eating disorders, running away from home, alcohol and drug abuse or sexual abuse. Psychoeducation in early-onset schizophrenia is a medical intervention that must be individually adapted to the phase of psychosis which may be prodromal, acute, stabilising or stable, and to the possibilities, needs or cultural setting. It can have a structured or unstructured form and be conducted in an individual or group setting. Psychoeducation will be accompanied by rehabilitation programmes, training in dealing with residual symptoms, improvement of cognitive processes (attention, memory, executive functions, social cognition), school support and psychosocial interventions [27, 54].

Prognosis and factors that influence recovery

Some researchers make an additional distinction between psychosis with its onset in childhood and the disease that has its onset in adolescence. Psychosis with a very early onset (under the age of 13 years) is characterised by a shorter period of untreated psychosis and a lower level of functioning in comparison with the early-onset disease [56]. On the other hand, a literature review indicates that early-onset psychotic disorder is characterised by a longer period of untreated psychosis in comparison with adults [57].

Díaz-Caneja et al. [58] conducted a literature review for predictors of outcome in the group of early-onset psychoses. The review included studies with a follow-up period of one year to 42 years. The predictive value of the age at onset of the symptoms and of the duration of untreated psychosis is worth noting. Among other predictors, the following seem to be the most important: diagnosis of a non-schizophrenia psychosis (a favourable predictor), better premorbid and baseline functioning, condition at discharge from hospital, severity of symptoms, especially the negative ones, using cannabinols and family history of psychotic disorders (an unfavourable predictor). Cognitive functioning during the follow-up period was related, in brief, to the quality of cognitive functioning at the beginning of the disease, but also to the level of premorbid adjustment and the severity of negative symptoms. Also most recent studies confirm the significance of premorbid functioning, duration of untreated psychosis and age at onset [59].

Downs et al. [60] analysed factors correlated to treatment failure in a group of 618 patients with early-onset psychoses. The most common cause of a switch to a different neuroleptic was insufficient efficacy in combination with the presence of adverse effects. The presence of negative symptoms made treatment failure more likely, although this was not directly related to the diagnosis of schizophrenia. On the other hand, in the aforementioned study of Díaz-Caneja et al. [58], lower quality of psychiatric care use in early-onset schizophrenia was associated with earlier onset of the disease and the presence of delusions.

However, the long-term prognosis in early-onset schizophrenia seems to change over the years. In a review of articles from 1980 to 2011, the overall treatment outcome and level of functioning were rated as good in 15.4% of patients with an initial diagnosis of early-onset schizophrenia, moderate in 24.5% and poor in 60.1% [5].

In turn, a paper published in 2020 presented the results of a 10-year follow-up of 65 patients diagnosed with EOS (age 7-17 years). In this group, ¼ of the patients used clozapine, 26% achieved economic independence, and 21% were married at some point in their lives. In that group, the age at onset did not turn out to be a predictor of the level of subsequent functioning [61]. More general data, but in a large group of patients (n=1,223 patients with EOS, mean follow-up period 9.5 years), obtained on the basis of a Danish registry, were presented by Vernal et al. [62]. Apart from stating the fact children and adolescents spent more days in the hospital than adults with the disease, the researchers found no evidence for a more serious course of EOS than schizophrenia with the onset in the typical period.

Interesting results were also presented by the Australian Early Psychosis Prevention and Intervention Centre. In a 2007 paper, researchers found no differences between the effect of treatment in the group of patients with psychosis with onset in the adolescence period and in the adult group [2]. Several years later, Amminger et al. [63] in a seven-year follow-up period found a more favourable course of the disease in patients with early-onset psychosis than in adult patients. Unfortunately, to the knowledge of the authors of that paper, no other centre has presented similarly optimistic results so far.

Development of antipsychotic pharmacological treatment for paediatric patients

The regulations for marketing of new medicines have changed over time. Previous regulations are reflected in the wide range of approved uses for the earliest discovered neuroleptics. In the later period, clinical trial subjects were mostly adults (the discussion of how much the sex balance was retained goes beyond the thematic scope of the present paper). The small number of marketing authorisation studies with the participation of children, although it may result from the desire to protect this group of patients, in fact leads to a situation of inequality in health: children and adolescents are deprived of access to the latest medicines, and if they do receive these products, it is an off-label use, which means that it is not supported by appropriate research. Therefore, in the recent years both the European Union [64] as well as the Food and Drug Administration in the United States [65] introduced an administrative obligation of evaluating the safety and efficacy of the newly marketed medicines also in the paediatric population. The possibility of exemption from this obligation exists in certain specific situations, for example in the case of medicines used only in adult diseases.

Some of the medicines used in Poland (olanzapine, quetiapine, risperidone), which are authorised in our country for use from the age of 18 years, in other regions of the world, for example in the United States, can be used in the paediatric population. However, this does not change the legal situation of Polish patients and a physician practising in Poland.

Among the compounds that have been placed on our market in the recent years, registration of lurasidone, which is authorised for use in schizophrenia from the age of 13 years, has brought an important change. On the other hand, cariprazine is authorised for use in patients from the age of 18 [35].

In addition to clinical trials of neuroleptics already in use, the US register of clinical trials (www.clinicaltrials.gov) includes studies that assess the safety and efficacy of the following antipsychotics in paediatric patients: brexiprazole, cariprazine, lutamperone and ulotaront (SEP-363856; patients recruited were aged 13-65 years). These studies are ongoing.

SEP-363856 seems to be a particularly interesting molecule. It is an agonist of TAAR1 (trace amine-associated receptor 1) and the 5-HT1A receptor. TAAR1 belongs to the family of receptors associated with G protein and its activation leads to modulation of dopaminergic and also serotoninergic and glutaminergic activity [66]. Therefore, it is a different mechanism of action than affinity to dopamine receptors that characterises other antipsychotics.

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Address: Małgorzata Janas-Kozik
Medical University of Silesia in Katowice
Clinical Department of Psychiatry and Psychotherapy of Developmental Age
Paediatric Centre in Sosnowiec
41-218 Sosnowiec, Gabrieli Zapolskiej Street 3
e-mail: janaskozik@gmail.com