

Recommendations for the treatment of schizophrenia with negative symptoms. Standards of pharmacotherapy by the Polish Psychiatric Association (Polskie Towarzystwo Psychiatryczne), part 2

Agata Szulc^{1,7}, Dominika Dudek^{2,7}, Jerzy Samochowiec^{3,7},
Marcin Wojnar^{4,7}, Janusz Heitzman^{5,7}, Piotr Gałęcki^{6,7}

¹ Medical University of Warsaw, Faculty of Health Sciences, Department of Psychiatry

² Jagiellonian University Medical College, Department of Adult Psychiatry

³ Pomeranian Medical University in Szczecin, Department of Psychiatry

⁴ Medical University of Warsaw, Department of Psychiatry

⁵ Institute of Psychiatry and Neurology, Department of Forensic Psychiatry

⁶ Medical University of Lodz, Department of Adult Psychiatry

⁷ Polish Psychiatric Association

Summary

Contemporary approach to schizophrenia treatment assumes multidirectional therapeutic intervention aimed at achieving full remission and the patient's return to full psychosocial functioning. Properly selected and administered pharmacotherapy still plays the key role in schizophrenia treatment. In previous decades (starting from the 1950s) the use of antipsychotics aimed mostly at managing positive symptoms (aggression, agitation). In subsequent decades (starting from the 1980s) it was possible to use new generation medications with fewer side effects. Some of those medications turned out to be also helpful in alleviating negative symptoms, which gave some patients an opportunity to return to normal functioning. Nevertheless, there is still a common belief that schizophrenia patients with predominant or persistent negative symptoms are the most serious challenge from the therapeutic perspective. They are characterized by worse course of the illness, poorer prognosis and response to treatment. There is constant need for new, more effective therapeutic interventions. The following paper presents international standards and recommendations of the Polish Psychiatric Association for effective approach to treating negative symptoms in schizophrenia.

Key words: schizophrenia, negative symptoms, treatment of schizophrenia

Introduction

Negative symptoms of schizophrenia are a serious diagnostic and clinical problem. The following paper presents recommendations on the treatment of schizophrenia with negative symptoms. The standards were developed by a group of experts from the Executive Board of the Polish Psychiatric Association (authors of the manuscript). Pharmacotherapy standards were based on the literature data and expert consensus.

The second part of the article presents a review of international recommendations and guidelines. In the summary of the paper, standards are presented as a practical algorithm for the treatment of schizophrenia with negative symptoms.

The greater part of the references, for editing reasons, was included in the first part of the recommendations.

1. International pharmacological standards in treating schizophrenia with negative symptoms

1.1. Practical recommendations issued by the American Psychiatric Association (APA)

Those recommendations are not particularly useful nowadays, since in spite of being formally published in 2010, they were actually developed in 2004 [1]. This is why they do not take account of a whole host of new medications.

The authors claim that now (i.e., during the period when standards were published) there are no methods to treat persistent negative symptoms. They encourage physicians to make their own searches and to eliminate factors leading to secondary negative symptoms. They believe that it is advisable to fight positive symptoms with antipsychotics, depression with antidepressants, anxiety with anti-anxiety agents, Parkinson's symptoms with anti-Parkinson's drugs, and generally extrapyramidal symptoms by reducing the doses of antipsychotics.

1.2. Recommendations of the World Federation of Societies of Biological Psychiatry (WFSBP)

The 2012–2013 WFSBP recommendations stress the need to avoid secondary negative symptoms and prefer atypical antipsychotic therapy to achieve it [2]. The recommendations refer to the clinical indication described as schizophrenia with 'predominant negative symptoms' (in the chapter devoted to 'specific clinical features influencing the treatment plan', part 1. WFSBP recommendations) [2].

Generally, the use of all atypical antipsychotics can help avoid extrapyramidal symptoms and consequently reduce secondary negative symptoms. When it comes to the management of primary negative symptoms, the highest recommendations were given only to amisulpride and olanzapine (category A, confirming efficacy of the therapy). There are some significant differences between part 1 and part 2 published

one year later, e.g., strengthening the position of aripiprazole in the management of negative symptoms [2].

1.3. NICE recommendations

In 2014, The British National Institute for Health and Care Excellence (NICE) published schizophrenia treatment recommendations referring also to the issue of negative symptoms.

The treatment of persistent negative symptoms is discussed in the chapter devoted to pharmacological therapy of schizophrenia in which a patient ‘has not adequately responded to treatment’ [3]. An analysis of studies from 1990–2007 was presented there, which is of little relevance at the time being and which includes 10 papers comparing the action of amisulpride, olanzapine, quetiapine, risperidone, ziprasidone, and classic antipsychotics. The treatment lasted from 6 weeks to one year, most often (the mode) for 12 weeks. It was established that trials conducted so far had not provided any evidence for differences in the efficacy of medications used to treat persistent negative symptoms. Also no differences in treatments with added antidepressants were revealed.

Furthermore, the NICE [4] has published only two recommendations on additional techniques supporting the therapy of persistent negative symptoms: art therapy – as a method of choice, and cognitive behavioral therapy (CBT).

Comprehensive approach to schizophrenia therapy from the cognitive behavioral perspective includes the following:

- establishing contact and building the therapeutic relation;
- explaining psychosis in the following categories: susceptibility–stress model, continuum of experience in normality, and psychosis and strengthening of compliance;
- analysis of factors preceding psychosis;
- therapy of concurrent anxiety and depression;
- building the sense of reality;
- work with enduring positive symptoms;
- work with negative symptoms;
- preventing relapses;
- consolidating the acquired skills.

1.4. Additional recommendations

All the standards stress the need for avoiding medications that induce and exacerbate secondary negative symptoms. It is commonly emphasized that pharmacological therapy should have individualized character (dose optimization, timing optimiza-

tion, optimal efficacy and tolerability ratio, taking into account factors affecting compliance). One of possible therapeutic methods is also the possibility to use deep brain stimulation.

Transcranial magnetic stimulation (TMS) is a relatively new technique of non-invasive brain stimulation which can be used in managing schizophrenia with predominant negative symptoms. It has been demonstrated that the cortex modulation caused by TMS is accompanied by changes in cognitive indicators related to negative symptoms of schizophrenia and reduction of illness symptoms in the PANSS [5, 6].

The need to consider rehabilitation – methods of psychosocial therapy, art therapy, cognitive behavioral psychotherapy, is also emphasized. The objectives of schizophrenia therapy might also be supported by psychoeducation, metacognitive training and avatar therapy. Rehabilitation activities are believed to be necessary, sufferers need to function in an enriched social system, their isolation needs to be interrupted, they have to be provided with occupation and get involved in anti-exclusion programs [3].

2. Recommendations for the therapy of schizophrenia with negative symptoms – pharmacotherapy standards developed by the expert group of the Executive Board of the Polish Psychiatric Association

In pharmacotherapy standards two populations of schizophrenia patients with negative symptoms should be distinguished: individuals with negative symptoms, as well as patients with predominant and persistent negative symptoms (for more details see the diagnostic criteria for the latter).

In order to ensure optimal conditions of pharmacological therapy, it is necessary to establish an individual therapeutic plan. The treatment should be comprised of many stages and modified depending on both the achieved or unachieved goals. Pharmacotherapy should take account of the combination of interventions of both pharmacological and psychosocial nature.

Figure 1 presents the general strategy for managing negative symptoms in schizophrenia.

PHARMACOTHERAPY – RECOMMENDATIONS

2.1. Schizophrenia with negative symptoms

Amisulpride

- For the population with predominant negative symptoms, the meta-analysis of series of trials has revealed higher reduction of their severity vs. placebo, but because of statistically significant difference in reducing depressive symptoms in some of those trials, it is impossible to indisputably decide whether in those cases the medication targets primary or secondary symptoms; the com-

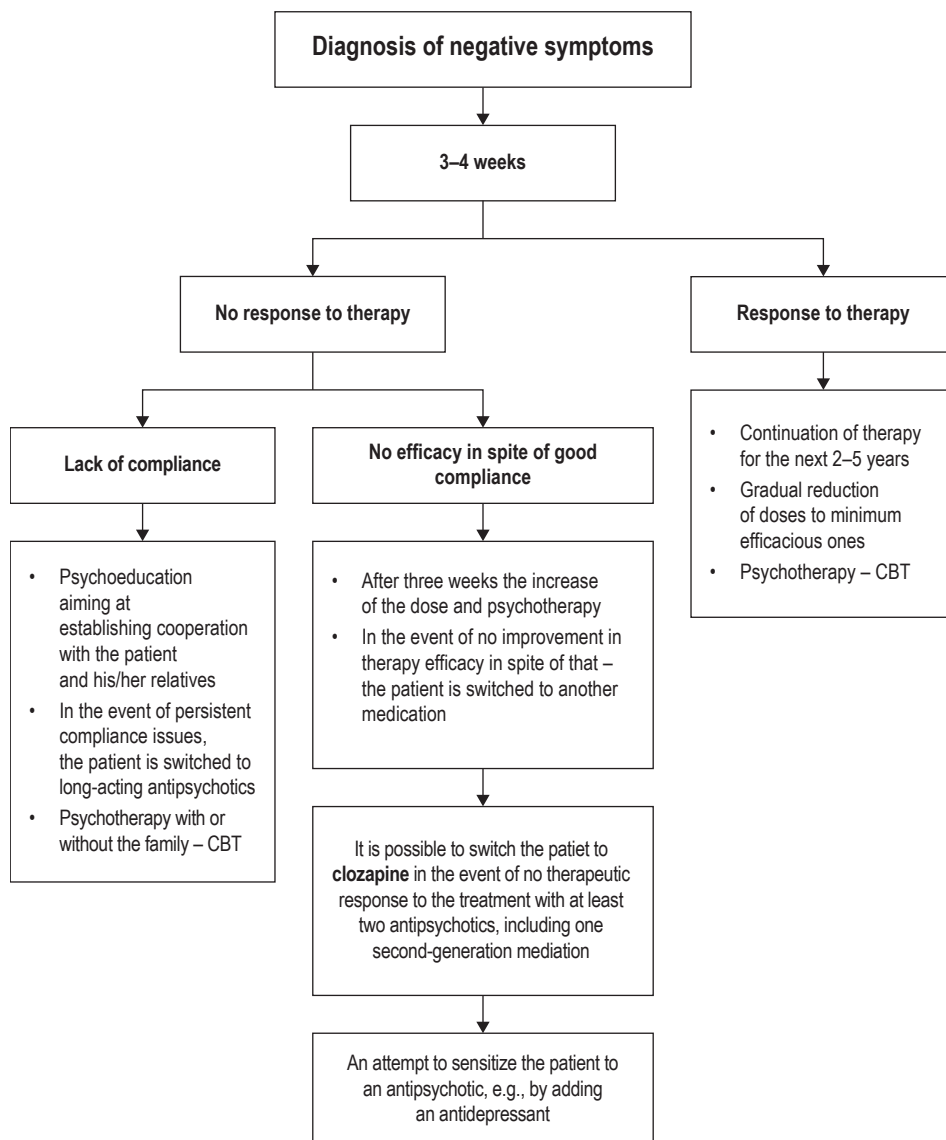


Figure 1. Therapeutic paradigm of managing patients with schizophrenia with negative symptoms [2–4; additional references are available in the part 1 of the standards]

parison to olanzapine in this patient population has not revealed any differences between medications;

- For the population with prominent negative symptoms, the available evidence indicates that there is no difference compared to fluphenazine, haloperidol or ziprasidone;

- The impact on the reduction of the severity of negative symptoms in the general population of schizophrenia sufferers, regardless of initial intensity, has been assessed in numerous randomized trials, the results of which tend to suggest higher efficacy of amisulpride vs. first-generation drugs and parity to second-generation drugs in this respect;
- Low dosing is recommended, i.e., 50–300 mg/daily. There is a risk of adverse events that can induce secondary negative symptoms. At higher doses the risk of extrapyramidal symptoms and metabolic disorders increases.

Aripiprazole

- There are no trials among the population of patients with predominant or prominent negative symptoms available for this medication;
- Available scientific evidence pertains to the impact on the reduction of the severity of negative symptoms in the general population of schizophrenia patients, and has demonstrated comparable or superior efficacy vs. first-generation medications as well as comparable efficacy vs. second-generation drugs;
- The medication has favorable safety profile; in patients with the illness stabilized with the oral aripiprazole doses, the extended-release IM formulation can be considered.

Clozapine

- There are no trials available for the population of patients with predominant negative symptoms;
- For the population with prominent negative symptoms (in this case the ‘deficit syndrome’ or high severity of negative symptoms) the results of two studies have not demonstrated any superiority of the drug over haloperidol;
- The impact on the reduction of the severity of negative symptoms in the general population of schizophrenia sufferers, regardless of their initial intensity, has been assessed in numerous randomized trials, the results of which largely suggest higher efficacy compared to first-generation drugs, and parity vs. second-generation medications;
- There is a high risk of agranulocytosis. The white blood count should be monitored during the therapy;
- The dose needs to be adjusted individually.

Quetiapine

- There are no trials available for the population of patients with predominant negative symptoms;
- For the population with prominent negative symptoms, the results of two trials indicate that there are no differences vs. olanzapine, whereas the results of the comparison vs. risperidone are not believed by authors of the trial to be

statistically significant (the data presented in the systematic review, which the WFSBP guidelines refer to, suggest the superiority of quetiapine);

- The impact on the reduction of the severity of negative symptoms in the general population of schizophrenia patients, regardless of initial severity, has been assessed in numerous randomized trials, the results of which tend to suggest comparable or higher efficacy of quetiapine vs. first-generation medications, and comparable efficacy vs. second-generation drugs;
- A low dose is required (300–450 mg/day). There is a high risk of metabolic disorders and sedation, and consequently also the development of secondary negative symptoms.

Lurasidone

- There are no trials available for the population of patients with predominant or prominent negative symptoms;
- Available scientific evidence pertains to the impact on the reduction of the severity of negative symptoms in general population (regardless of their severity), while the results for the comparison to placebo are inconsistent and have revealed the lack of differences or an advantage of lurasidone, whereas single trials comparing it against second-generation medications have virtually not revealed any significant differences;
- There is a risk of increased prolactin concentration, body weight gain and sedation, and consequently also development of secondary negative symptoms.

Olanzapine

- There are three trials available for the population with predominant negative symptoms. None of them has demonstrated any differences compared to amisulpride or asenapine, yet they have revealed superiority over haloperidol. The results of the comparison against placebo are ambiguous, and depending on the utilized data analysis method and the dose of the medication, they have either revealed no differences or superiority of olanzapine;
- In the population with prominent negative symptoms, there have not been any differences vs. quetiapine, whereas olanzapine has proven to be superior to risperidone; moreover, the results for subgroups in one of the studies reveal the superiority of haloperidol, but only for one of the highest analyzed doses and for selected components of the SANS scale;
- The remaining data concerning the impact on reducing the severity of negative symptoms in the general population (regardless of intensity), and for the comparison to first-generation drugs largely prove the superiority of olanzapine, yet it is noteworthy that in one of the trials in which the advantage of olanzapine over haloperidol and risperidone has been demonstrated, once the results were adjusted taking account of confounding factors related to secondary negative symptoms, the results were no longer statistically significant;

the lack of differences vs. risperidone and other second-generation drugs has been confirmed by numerous trials;

- The administration of low doses (5 mg/day) is recommended. There is a high risk of metabolic disorders and sedation, and consequently also of the development of secondary negative symptoms;
- For patients whose illness has been stabilized by means of oral doses of olanzapine, the extended-release IM formulation can be considered.

Paliperidone

- For this medication there are no trials designed to assess its efficacy in the population of patients with predominant negative symptoms, yet aggregated data from three trials have allowed for isolating the results for patient subgroups with predominant negative symptoms, and the results of this analysis demonstrate the superiority of paliperidone over placebo;
- Few trials allowing for assessing the impact on negative symptoms compared to second-generation drugs are not fully consistent, but they generally demonstrate comparable efficacy;
- For patients who have responded to oral paliperidone or risperidone therapy, extended-release IM injections can be considered.

Risperidone

- For the population with predominant negative symptoms, the results of one trial have demonstrated higher efficacy of cariprazine compared to risperidone;
- For the population with prominent negative symptoms, the results of three trials are available, and they demonstrate nominal advantage of risperidone, no statistically significant differences vs. flupentixol and advantage of olanzapine (but the results of comparisons against olanzapine are burdened with certain uncertainty – described in the subchapter devoted to olanzapine in part 1). One trial comparing it to quetiapine is believed by the authors not to demonstrate any differences between groups (data presented in the systematic review, which the WFSBP guidelines refer to, among others, suggest the superiority of quetiapine);
- There are many results referring to the impact on changes in the severity of negative symptoms in the general population of schizophrenia patients (regardless of intensity), and they demonstrate the advantage of risperidone over first-generation drugs and no differences vs. second-generation medications;
- The highest clinical efficacy can be observed for the 4–6 mg doses. Exceeding the 6 mg dose is related to a high increase of the risk of extrapyramidal symptoms;

- There is a high risk of increased prolactin concentration in blood, and increased body weight;
- In non-compliant patients it is possible to consider the extended-release IM formulation.

Sertindole

- There are no trials for the population of patients with predominant or prominent negative symptoms;
- Little evidence for the efficacy of sertindole in reducing the severity of negative symptoms in general population (regardless of their initial intensity) has not demonstrated any significant differences vs. either first – or second-generation medications;
- It is necessary to monitor the ECG during the therapy. High risk of QT interval prolongation;
- The treatment should be initiated from the 4 mg/day dose. The initial dose of 8 mg or fast increase of the dose are related to considerably higher risk of orthostatic hypotony.

Ziprasidone

- There are no trials for the population with predominant negative symptoms available for this medication;
- There is only one trial available for the population with prominent negative symptoms, and it has not demonstrated any differences vs. amisulpride;
- Relatively little evidence for the impact on the reduction of negative symptoms in the general population of schizophrenia patients suggests either no difference or superiority over first-generation drugs and no difference vs. second-generation medications;
- The risk of QT interval prolongation;
- In schizophrenia maintenance therapy the lowest effective dose should be selected; in many cases 20 mg administered twice daily is sufficient.

Polytherapy: antipsychotic + antidepressant

- Study results are ambiguous, in spite of high popularity of this method. Probable beneficial effects with the use of catecholaminergic antidepressants (reboxetine, bupropion, mirtazapine).
- Confirmed relative safety of the combination of antipsychotics and antidepressants [7].

Polytherapy: antipsychotic + an anti-inflammatory drug

- Experimental trial (minocycline, celecoxib, acetylsalicylic acid);

- Concerns medications registered for other indications; safety of the therapy has not been confirmed in proper conditions.

Polytherapy: antipsychotic + psychostimulant

- Experimental trial (lisdexamfetamine, modafinil and armodafinil);
- Concerns medications registered for other indications; safety of the therapy has not been confirmed in proper conditions.

Polytherapy: antipsychotic+ memantine

- Experimental trials;
- Concerns medications registered for other indications; safety of the therapy has not been confirmed in proper conditions.

Polytherapy: The most commonly used combination is clozapine + another antipsychotic drug

2.2. Schizophrenia with predominant and persistent negative symptoms

Diagnostic criteria:

- a) chronic negative symptoms for at least 6 months;
- b) The following number of points in the Questionnaire Assessing Predominant Negative Symptoms:
 - i. the sum of points in the negative symptom scale ≥ 24
 - ii. 3 following criteria from the subscale for negative symptoms assessed at ≥ 4
 - blunted affect
 - avolition
 - no spontaneity/fluency in conversation
 - i. the sum of points in the positive symptom scale ≤ 19

(For the Questionnaire Assessing Predominant Negative Symptoms see Appendix 1).

Cariprazine

- It is the only medication among the explored ones that has a trial demonstrating statistically significant advantage over another second-generation medication in the population of patients with predominant negative symptoms in whom such a clinical condition has been stable for at least 6 months (patients with secondary negative symptoms caused by depressive disorders and drug-induced Parkinson's symptoms were excluded from the study, which allows for concluding that the medication affects the reduction of primary negative symptoms to some extent);
- The remaining scientific evidence pertains to the total population for which the advantage of cariprazine over placebo in reducing negative symptoms has been demonstrated;

- The medication has favorable safety profile.

2.3. Additional recommendations

1. In order to ensure optimal conditions for pharmacological therapy of negative symptoms, it is necessary to:
 - a) achieve remission within the following clinical areas:
 - i. positive symptoms;
 - ii. extrapyramidal symptoms;
 - iii. depressive symptoms;
 - iv. drug-induced activity disorders (akinesia, sedation).
 - b) to tailor the therapy to the phase (acute episode, consolidation, stabilization, and remission) via:
 - i. monitoring psychopathological symptoms and adverse events;
 - ii. implementing the therapy plan with a given medication according to Figure 2;
 - iii. verifying the ability to achieve psychosocial functioning goals, regardless of the quality of life assessment.
2. It is necessary to activate an auxiliary psychosocial support program, including:
 - a) implementation of the psychoeducation program for patients and their families (caregivers);
 - b) the use of psychotherapeutic techniques of relatively highest efficacy, including:
 - i. Cognitive behavioral therapy (CBT);
 - c) patients' participation in the supported employment program;
 - d) patients' participation in environmental support programs, ensured by both institutional and non-institutional entities.
3. At the diagnostic and maintenance stage it is necessary to:
 - a) have the following tests: ECG, full blood count, blood pressure, creatinine level in serum, electrolyte concentration;
 - b) quit smoking;
 - c) systematic monitoring of: the BMI, metabolic profile (glucose level, HbA1C) and lipid profile (LDL, HDL, triglycerides), waist size, prolactin level.
4. It is desirable to introduce healthy lifestyle – to increase physical activity and implement optimal dietary habits.

3. Recapitulation

The efficacy of antipsychotic treatment of acute psychotic disorders, mainly positive symptoms, is described in schizophrenia as limited, but in reality what is even more limited is the efficacy of treating chronic disorders, especially those with predominant negative symptoms [8]. The negative aspect of the illness can be most important in the entire prognosis. In the long-term perspective, the ability to achieve

functional improvement will in practice be determined by the ability to reduce negative symptoms. Such an opportunity is offered by novel antipsychotics: partial dopamine agonists (D2, D3) and serotonin ones (5-HT1A) [9].

Each atypical antipsychotic has its profile of receptor binding which differentiates it from the remaining antipsychotics. The unique profile of the bonding for each antipsychotic affects the efficacy in reducing negative symptoms and the likelihood to cause side effects. The receptor profile of an antipsychotic in reducing negative symptoms should be related to partial agonism of D2/D3 dopamine receptors, action targeted at limbic and cortical D3 dopamine receptors, as well as stimulation of 5-HT1A serotonin receptors. For the elements of the receptor profile of antipsychotics, see Table 1.

Novel medications are not only likely to reduce the risk of inducing secondary negative symptoms, but first of all they offer active reduction of primary ones.

The practical algorithm of pharmacotherapy of schizophrenia with negative symptoms, depending on the identified diagnostic criteria and illness duration is presented in Figure 2.

Table 1. Strength of the bond between receptors and antipsychotics from the serotonin and dopamine antagonist group [11]

Medication	D						5-HT										α		
	1	2	3	4	1A	1A	1D	2A	2B	2C	3	6	7	M1	H1	1	2	SRI	NRI
amisulpride		XX_X	XXX					XX	XX				XX						
aripiprazole		XX_X	XXX		XXX	XX	XX	XXXX					XXX		XX	XX	XX		
cariprazine		XX_XX	XXXX		XXX		XX	XXXX	X				X		XX	X			
lurasidone		X		XXXX	XXX		X						XXXX			XX	XX		
asenapine	XXX	XX_X	XXX	XXXX		XXX	XXXX	XXX	XXXX	X		XXXX	XXXX	X	XXX	XXX	XXX		
sertindole	X	XX_X	XXX	XXX	X		XXXX		XXX			XXX	XX		X	XXX			
paliperidone		X					X						X		XX	X			
clozapine	X	X_	X	XX	X		XX	XXX	XX	X		XX	XX	XXX	X	XXX	XXX		
risperidone	X	XX_X	XXX	XXX		X	XXXX	XX	XX				XXX		XX	XXX	XXX		
olanzapine	XX	X_X	XX	XX		X	XXX	XX	X	X		XX	X	XX	XXX	XX	XX		
quetiapine	X	X_	X			X	XX	XX	X			X	XX		XXX	XXX	X		
ziprasidone		XX_X	XXX		X	XXX	XXXX	XX	XX	XX		XX	XXX		XX	XX	XX	X	X

* _ – partial agonism; D – dopaminergic; 5-HT – serotonergic (5-hydroxytryptamine); M – muscarinic; H – histamine; α – alpha-adrenergic (norepinephrine); SRI – serotonin reuptake inhibition, NRI – norepinephrine reuptake inhibition

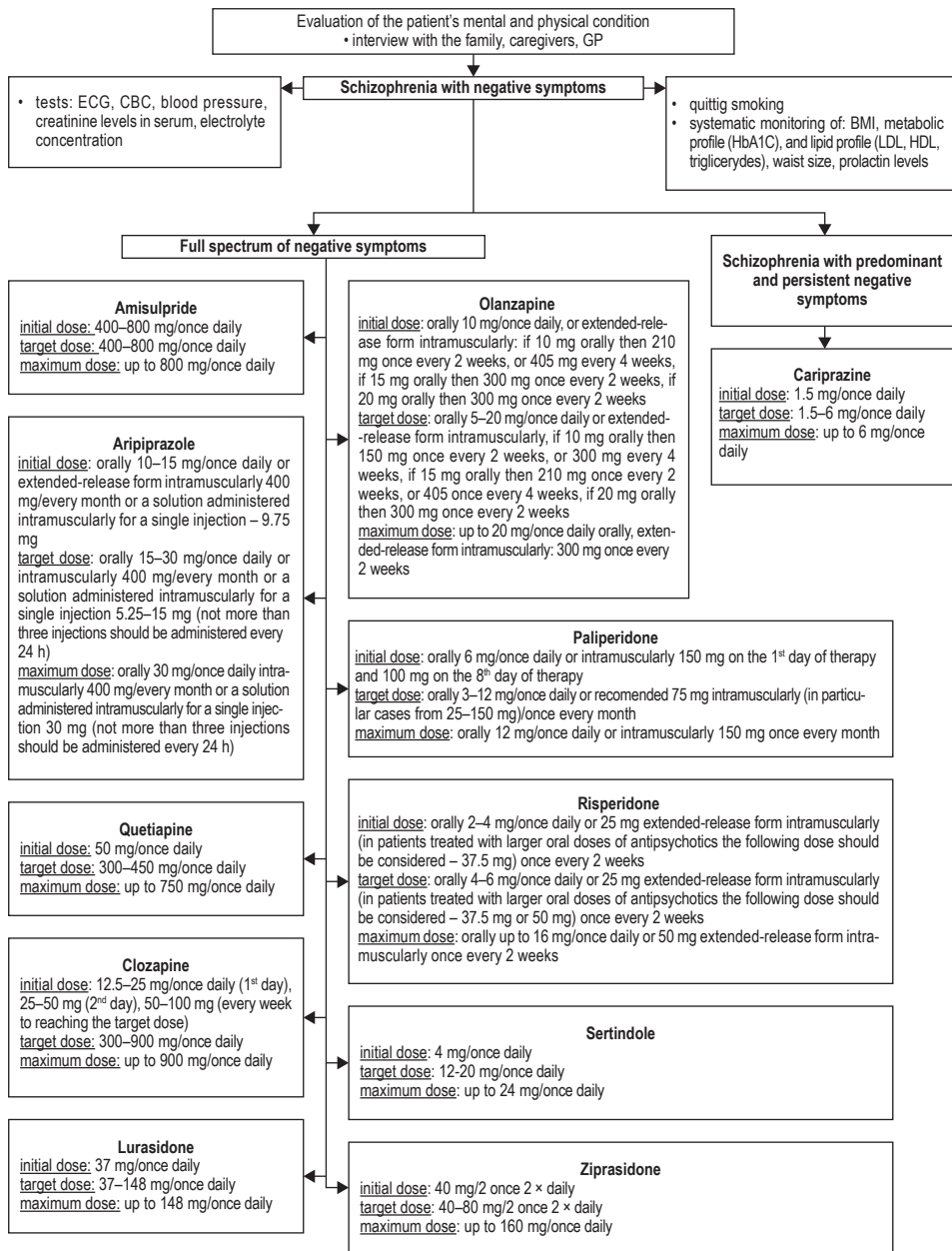


Figure 2. Pharmacotherapeutic paradigm in schizophrenia: with negative symptoms and with predominant and persistent negative symptoms – standards by the Polish Psychiatric Association [10; additional references are available in part 1 of the standards]

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Address: Agata Szulc
Department of Psychiatry, Faculty of Health Sciences
Medical University of Warsaw,
05-802 Pruszków, Partyzantów Street 2/4
e-mail: aszulc@wum.edu.pl

Appendix 1

QUESTIONNAIRE UTILIZED TO ASSESS PREDOMINANT NEGATIVE SYMPTOMS

Assess the intensity of each of the following symptoms, using a scale from 1 to 7, where 1 means no symptom at all, and 7 – the highest intensity of a given symptom.

Negative symptoms: blunted affect, emotional withdrawal, poor contact with others, avolition, no spontaneity/fluency in discussion, slow motion, asociality

Positive symptoms: delusions, abnormal thought contents, hallucinations, grandiose delusions, conviction about being persecuted/suspiciousness.

In order to diagnose a patient with predominant negative symptoms, a patient should achieve the following results:

- the sum of points for negative symptoms ≥ 24
- 3 following criteria from the negative symptom subscale assessed at ≥ 4
 - blunted affect
 - avolition
 - no spontaneity/fluency in conversation
- the sum of points for positive symptoms ≤ 19 .

In order for negative symptoms to be considered persistent, they should pertain for at least 6 months.