

Recommendations for the treatment of schizophrenia with negative symptoms. Standards of pharmacotherapy by the Polish Psychiatric Association (Polskie Towarzystwo Psychiatryczne), part 1

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Summary

Schizophrenia is a chronic illness that in the majority of cases begins either in adolescence or early adulthood. It is often perceived as a severe, incurable condition with generally poor prognosis, while patients suffering from it tend to be agitated, aggressive and unpredictable in their behaviors. Growing awareness, along with gradual changes in the approach to the need for multifaceted schizophrenia therapy, as well as considerable progress in pharmacotherapy in recent years have allowed for improving the prognosis for many patients. Because of polymorphic character of the condition, many schizophrenia sub-types are identified by means of classifications of mental disorders, adjusting the criteria and descriptions to most frequently observed clinical scenarios. Clinical descriptions of schizophrenia are based on various psychopathological models, which are often multidimensional and multifactorial. They virtually always take account of the following two dimensions: negative (deficit) and positive (creative) symptoms. Contemporary approach to schizophrenia treatment assumes multidirectional therapeutic intervention aimed at achieving full remission and the patient's return to full psychosocial functioning. Long-term studies indicate that the severity of negative symptoms is the prognostic indicator of the deterioration of social and professional functioning and reduced quality of life. The following paper presents the review of concepts and research devoted to negative symptoms in schizophrenia and their treatment; in the second part, international standards and recommendations of the Polish Psychiatric

Association concerning the approach to effective management of negative symptoms in schizophrenia are discussed.

Key words: schizophrenia, negative symptoms, treatment of schizophrenia

Introduction

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

The first part of the article presents a review of the literature on which recommendations were based.

1. The diagnostic process and the occurrence of negative symptoms of schizophrenia

The diagnosis of negative symptoms includes the following deficits:

- diminished emotional expression (blunting of affect leading to the ‘mask-like face’ effect);
- inability to experience pleasure (anhedonia);
- poverty of speech, both as regards words and communicated content (alogia);
- reduced social needs, isolation from others;
- lack of initiative to make attempts to achieve something (avolition) [1–4].

In order to diagnose negative symptoms, it is necessary to make the following two clinical distinctions:

- 1) between primary and secondary negative symptoms;
- 2) between the negative dimension and other aspects of schizophrenia.

By eliminating unfavorable iatrogenic effects, e.g., caused by antipsychotics (sedation, akinesia, autonomic symptoms, extrapyramidal symptoms) and preventing social isolation, it is possible to create favorable conditions for secondary negative symptoms to subside.

Differentiating between negative symptoms and cognitive function deficit or depressive symptoms might be challenging [5, 6]. The correlation of results of the neurocognitive scales and negative symptoms is very close – also in those patients who have so far not been treated, so the distinction results more from the conceptual decisions about separating those phenomena rather than natural dissimilarities between them [6].

The differentiation between negative symptoms and depressive disorders is different. Unlike the neurocognitive scales results, depressive disorders in schizophrenia do not significantly correlate with negative symptoms [5]. Helpful diagnostic tools have been developed, namely the MTSD (Maryland Trait and State Depression) scale

which allows for isolating both transient and persistent depressive conditions from the clinical picture of schizophrenia patients [5].

1.1. Diagnostic scales

There is no one, unanimously acclaimed diagnostic tool for diagnosing schizophrenia with predominant negative symptoms. Initially the first scales commonly used to assess schizophrenia symptoms (referred to as first-generation scales) took account of negative symptoms as an element of the comprehensive profile of the illness. Second-generation scales were developed later, following the Consensus Development Conference on Negative Symptoms held in 2005, during which experts decided to standardize negative symptoms and based on that they defined assumptions necessary to create new diagnostic scales.

First-generation scales used most often in clinical trials include the PANSS and the SANSS, i.e., the Positive and Negative Syndrome Scale, dividing 30 selected symptoms into three groups: 7 positive, 7 negative and 16 general, and the Scale for the Assessment of Negative Symptoms, describing seven domains: alogia (poverty of thinking), affective flattening, attention disorders, avolition and apathy, anhedonia and asociality [7, 8].

The most popular second-generation scale is the Brief Negative Symptom Scale (BNSS), developed in 2011, taking the form of an interview. This scale assesses five symptoms recognized during the Consensus Development Conference on Negative Symptoms – anhedonia, social withdrawal, avolition, affective flattening, and alogia. Apart from that, the 6th subclass describing mental suffering, i.e., worrying, was identified.

In clinical trials PANSS and SANS scales and tools based on them are used the most often.

Table 1. **First-generation scales used to assess negative symptoms**

Scales	Authors	Year
Brief Psychiatric Rating Scale (BPRS)	Overall, Gorham	1962
Positive and Negative Syndrome Scale (PANSS)	Kay, Fiszbein, Opler	1987
Scale for Assessment of Negative Symptoms (SANS)	Andreasen	1989
Schedule for the Deficit Syndrome (SDS)	Kirkpatrick et al.	1989

Source: prepared based on [8].

Table 2. **Second-generation scales used to assess negative symptoms**

Scales	Authors	Year
Clinical scales		
Clinical Assessment Interview for Negative Symptoms (CAINS)	Kring et al.	2013
Brief Negative Symptom Scale (BNSS)	Kirkpatrick et al.	2011

table continued on the next page

Self-assessment scales		
Motivation and Pleasure Scale – Self Report (MAP-SR)	Llerena et al.	2013
Self-assessment of Negative Symptoms (SNS)	Dollfus et al.	2016

Source: prepared based on [8].

2. Prevalence of negative symptoms in the schizophrenia patient population

In recent period a host of large epidemiological studies devoted to negative symptoms have been carried out, assessing their prevalence at the level:

- 52.5% – at least one symptom in the population of 1,120 patients [9]; the diagnosed symptoms come from the PANSS scale;
- 57.6% – at least one symptom in the population of 1,108 patients [10]; 5 symptoms from the PANSS negative symptom scale: with severity >3, and at the same time <3 in the case of any positive symptom, ≤3 in the case of anxiety or depressive symptoms;
- 41% – at least 2 negative symptoms in the population of 7,678 patients [11]; the symptoms were collected automatically by means of electronic documentation, with the annual assessment;
- 23.7% – in the population of 138 patients with the first psychotic episode [12], broken down into groups with persistent negative symptoms and other than persistent negative symptoms;
- 25–30% – primary persistent negative symptoms [13].

3. Schizophrenia with negative symptoms

The classic dichotomy, a concept that is over 100-years-old, divided schizophrenia into paranoid-type and simple-type (with predominant negative symptoms). This division is largely still employed in the ICD-10. At the same time, in the American diagnostic system (DSM-5) rather the dimensional clinical description is used.

Enthusiasts of the concept of a separate nosological entity, namely schizophrenia with predominant negative symptoms, have proposed more models, turning a loose collection of symptoms into a consistent set [14]. According to the classification proposed in the publication by Marder et al. [15], there are two categories of patients: with predominant negative symptoms and with prominent negative symptoms. Such symptoms were defined as predominant in a situation in which patients could suffer from other symptoms, especially positive, yet their severity was relatively low, and they were properly controlled. At the same time, patients with prominent negative symptoms were defined as ones suffering from severe negative symptoms, regardless of how severe the positive ones were.

3.1. The criteria of defining schizophrenia with predominant negative symptoms and persistent negative symptoms – assumed in clinical trials

1. The full subscale of the PANSS negative symptoms:
 - a) based on the proportion of schizophrenia with predominant negative symptoms (42.3%) compared to schizophrenia with predominant positive symptoms (57.7%) [16];
 - b) based on prominent and predominant negative symptoms, the 2-stage concept:
 - i. ‘prominent’ negative symptoms are at least 3 symptoms with ≥ 4 scores, or 2 with ≥ 5 scores, calculated based on the PANSS negative symptom subscale [17];
 - ii. it can be additionally assumed that negative symptoms are ‘predominant’ if the sum of points of the PANSS positive symptom subscale is < 19 [4];
 - c) point advantage (the N-P difference) between relevant PANSS subscales [4];
2. Results of the PANSS scale after their factorial transformation:
 - a) set of negative symptoms: N1, N2, N3, N4, N6, G7, G16 [9];
 - b) two factors of negative symptoms, defined by means of selected PANSS symptoms [18]:
 - i. N2, N4, G16 – a factor responsible for social and emotional functioning; social amotivation;
 - ii. N1, N3, N6, G5, G7, G13 – a factor responsible for the level of coping in everyday life; expressive deficits;
3. Criteria defining prevalence of negative symptoms [4]:
 - a) the severity of negative symptoms is moderate for at least 3 of them, or moderately severe for at least 2 of them;
 - b) the result for the PANSS negative symptom subscale exceeding the result for the positive symptom subscale;
 - c) any result in the PANSS negative symptom subscale, but at least 6 points higher than in the positive symptom subscale;
 - d) at least 21 points in the PANSS negative symptom subscale, and at least one point more than in the PANSS positive symptom subscale;
 - e) severity of symptoms for points a) and b) is defined as obtaining not more than 19 points in the PANSS positive symptom subscale; depression and extrapyramidal symptoms below the threshold defined in the developed evaluation scale.
 - f) The duration of symptoms is not defined.
4. Criteria defining persistence of negative symptoms (PNS).

The mainly scientific concept utilized to standardize clinical trials [19] emphasizes the difference between persistent and transient negative symptoms. PNS is often accompanied by drug resistance [4].

The PNS definition includes the following criteria [19]:

- a) severity of negative symptoms is at least moderate;
- b) they persist chronically for at least 6 months,

- c) they can be accompanied by positive, depressive or extrapyramidal symptoms of low severity.

In scientific literature, there are numerous terms used to describe negative symptoms, which leads to inconsistencies in comparisons between study results. Discrepancies pertain to the selected set of symptoms as well as severity and duration of disorders.

The NICE uses the 'persistent negative symptoms' phrase (Appendix 23c) [20], even in relation to works in which a different expression was used such as 'predominant negative symptoms' – e.g., in the paper comparing the efficacy of olanzapine and amisulpride therapy [21]. The expression 'persistent' refers chiefly to duration of symptoms, while the 'predominant' one – to high severity of disorders. Other expressions, such as 'enduring' are to distinguish primary negative symptoms from more changeable over time persistent ones [14].

3.2. The profile and prognosis of schizophrenia patients with predominant and persistent negative symptoms

The results of studies conducted by various centers indicate that compared to other schizophrenia subjects, patients with predominant and persistent negative symptoms have poorer prognosis and are more often treatment refractory [10, 22]. In the group of 1,427 patients, primary negative symptoms statistically significantly worsened virtually every domain of functioning [23].

Compared to individuals with non-deficit forms of schizophrenia, the direct costs, cost of psychiatric therapy and the cost of non-psychiatric services offered to patients with prominent negative schizophrenia symptoms is estimated at a higher level [9]. Such patients, among others, require home visits, longer hospitalization at psychiatric wards, they are more vulnerable to suicide, homelessness, alcohol addiction, harmful use of psychoactive agents, loss of relations and social exclusion.

4. Pharmacological treatment of negative schizophrenia symptoms – data review

The level of interest in the efficacy of pharmacotherapy in managing negative symptoms of schizophrenia has considerably increased over the last years. It is not possible to achieve functional remission in patients without an improvement of negative symptoms [24].

Recent studies indicate that fast onset of therapy with the use of novel antipsychotic medications significantly reduces the risk of negative symptoms and raises the threshold of achievable clinical improvement [4].

4.1. Atypical antipsychotics

The efficacy of antipsychotics has been assessed in numerous systematic reviews, but few of them only comprehensively evaluated the impact of medications on reducing

the severity of negative symptoms. Available publications stress the fact that because of the lack of consensus, both as regards the definition and categorization of negative symptoms, and highly diversified research methodology, any conclusions concerning the efficacy of medications in this group of patients are considerably hindered. This is believed to result mostly from a very small number of studies in which their efficacy in treating schizophrenia with predominant or prominent negative symptoms is assessed. Most available publications pertain to the population of patients with illness exacerbation, suffering from predominant positive symptoms, and it is not obvious if the impact on negative symptoms is not related to larger extent to reduced severity of positive symptoms.

The key publication comprehensively analyzing the results of available studies in the population of patients with predominant or prominent negative symptoms is the systematic review by Krause et al. [25]. The search within the review included 34 antipsychotics (registered by the FDA or the EMA), and the inclusion criteria took account of randomized studies in which the assessed medications were compared to one another or vs. placebo. According to the classification proposed in the publication by Marder et al. [15], all studies were split into two categories: (1) those devoted to the population of patients with predominant negative symptoms and (2) those devoted to the population of patients with prominent negative symptoms. Symptoms were defined as predominant in a situation in which patients could also suffer from other symptoms, especially positive, but their severity was relatively low and they were properly controlled. On the other hand, the population with prominent negative symptoms was defined in a situation of high severity of negative symptoms, regardless of the severity of positive ones.

In the following part of the paper, in reference to individual medications, first of all information about available scientific evidence for the population with predominant or prominent negative symptoms will be presented, only then followed by data pertaining to the treatment of negative symptoms in a wider population of patients. Due to the fact that for the investigated condition there are hundreds of randomized studies available, in which one of the assessed end points was the impact on negative symptoms, it seems more justified to draw conclusions based on the available secondary papers in which the identified results of primary studies are accumulated.

The review below does not include first-generation drugs – on the one hand, literature data do not indicate their advantage over new generation drugs, and on the other hand there is a lot of evidence pointing to an unfavorable profile of side effects and poorer tolerance.

4.1.1. Amisulpride

The results of the meta-analysis of 4 studies (systematic review by Krause et al. [25]), including patients with predominant negative symptoms, have demonstrated a statistically significant superiority of amisulpride over placebo in the reduction of negative symptoms. In three out of all included studies [26–28] statistically significant superiority of amisulpride has been demonstrated, while in one study, Lecrubier et al.

[21], such superiority has not been confirmed (authors of the review suggest that it is the only study not sponsored by the manufacturer of amisulpride). This review also assesses the impact of medications on depressive and positive symptoms. A significant change has also been demonstrated for amisulpride as regards depressive symptoms, which is believed by the authors of this publication to indicate that it is not obvious whether this medication targets primary or secondary negative symptoms. For the population suffering from predominant negative symptoms the results of the aforementioned study by Lecrubier et al. [21] are also available, with amisulpride being compared to olanzapine. Here no statistically significant difference between those two medications in terms of their efficacy in reducing negative symptoms has been demonstrated.

At the same time, for the population of patients with prominent negative symptoms the analysis of results of the study by Saletu et al. [29] has not revealed any statistically significant differences between amisulpride and fluphenazine; the results of the studies by Speller et al. [30] and Olié et al. [31] demonstrate the lack of differences compared to haloperidol and ziprasidone, respectively.

The results of systematic reviews by Fusar-Poli et al. [32] and Leucht et al. [33] assessing the impact of various interventions on the reduction of negative symptoms against placebo have confirmed the aforementioned findings regarding statistically significant superiority of amisulpride over placebo in the population of patients with predominant negative symptoms. Both meta-analyses additionally take into account the results of the study by Paillère-Martinot et al. [34], which have been excluded from the review by Krause et al. [25] because of the manner in which the population is defined there. Nevertheless the authors of this study stress that it pertains to the population with primary negative symptoms. The results described in the study and in another review are on the verge of statistical insignificance for the PANSS scale total score (given significant superiority of amisulpride for three components of the scale), whereas the analysis in systematic reviews carried out by means of other statistical parameters demonstrates the superiority of amisulpride.

The above results refer to the population with predominant or prominent negative symptoms. As regards the impact on negative symptoms in a wider population (i.e., patients regardless of the severity of negative symptoms), the meta-analysis by Leucht et al. [35] indicates that based on the results of 10 studies statistically significant superiority of amisulpride over the first-generation medications in reducing negative symptoms in schizophrenia patients can be demonstrated. Nevertheless, a similar superiority of amisulpride in reducing negative symptoms has not been demonstrated in the meta-analysis by Leucht et al. [36] investigating the results of studies directly comparing amisulpride to the second-generation of medications (olanzapine – meta-analysis of 4 studies, risperidone – meta-analysis of 3 studies, ziprasidone – 1 study).

4.1.2. Aripiprazole

The systematic review by Krause et al. [25] has not identified any studies in which the impact of aripiprazole on the reduction of negative symptoms in the population of patients with predominant or prominent negative symptoms is assessed. Hence,

the available scientific evidence for this medication pertains to the total population of schizophrenia patients, within which the impact of aripiprazole on negative symptoms is assessed. The outcomes of the meta-analyses by Leucht et al. [33] and Fusar-Poli et al. [32] demonstrate a statistically significant superiority of aripiprazole over placebo in reducing negative symptoms. Those results are confirmed by the data obtained in later studies [37–40].

At the same time, the results of the meta-analysis by Leucht et al. [35] indicate that based on the outcomes of 5 studies it is impossible to conclude about statistically significant advantage of aripiprazole over first-generation medications in reducing negative symptoms in schizophrenia patients (the results are on the verge of insignificance). But it cannot be confirmed by long-term data for the observation period of 52 weeks [41] in which statistically significant advantage of aripiprazole over haloperidol in the population of exacerbated patients at an early stage of the illness has been demonstrated.

In a direct comparison to a second-generation medication (risperidone), the meta-analysis of the results of two studies has not revealed any substantial differences in reduction of negative symptoms [36]. No difference vs. risperidone has also been demonstrated in later studies [42–46]. The comparison to other second-generation medications (quetiapine, ziprasidone, olanzapine) has confirmed the obtained results [46–49].

4.1.3. *Cariprazine*

The systematic review by Krause et al. [25] has identified one study for the population of patients with predominant and persistent (at least 6 months) negative symptoms [50]. In this study, statistically significant superiority of cariprazine over risperidone in reducing negative symptoms has been demonstrated. At the same time, the impact of both medications on positive and depressive symptoms is comparable. It is the largest of all studies included in the review (461 patients), and according to the FDA [51] opinion, the observation period is long enough to assess the impact of medications on reducing the severity of negative symptoms.

The study inclusion criteria [50] included:

- 1) high severity of negative symptoms (affective flattening, avolition, no spontaneity/fluency in a conversation) and low intensity of positive symptoms;
- 2) stable clinical condition for at least 6 months;

The study excluded patients with secondary negative symptoms caused by:

- a) depressive disorders – moderate to severe;
- b) drug-induced Parkinson's symptoms.

Among all studies included in the review by Krause et al. [25], for predominant negative symptoms, only the studies by Németh et al. [50] and Lindenmayer et al. [52] have demonstrated the advantage of the medication over other active intervention, yet according to the authors of the review, the results of the study by Lindenmayer et al.

pertained to a very small population (35 patients), which is why they require further validation.

The remaining scientific results for cariprazine pertain to the total population of schizophrenia patients, for which the meta-analysis of 4 short-term studies has demonstrated a statistically significant advantage of cariprazine over placebo [53].

4.1.4. Clozapine

The systematic review by Krause et al. [25] has identified one study [54] in which the impact of clozapine on reduction of negative symptoms in the population of patients with prominent negative symptoms has been explored. This study has not demonstrated statistically significant advantage of clozapine over haloperidol in reducing the severity of primary or secondary negative symptoms. Just like in another study, no statistically significant difference in the comparison of clozapine and haloperidol in reducing negative symptoms in refractory patients has been revealed [55].

The remaining identified scientific evidence of clozapine efficacy in reducing the severity of negative symptoms refers to the general population of schizophrenia patients. The meta-analysis of results of 11 studies has demonstrated statistically significant superiority of clozapine over placebo in reducing the severity of negative symptoms [33]. The results of another meta-analysis by Leucht et al. [35] indicate, at the same time, that based on the results of 17 studies statistically significant advantage of clozapine over first-generation drugs in reducing negative symptoms in schizophrenia patients can be demonstrated. The direct comparison to second-generation medications (olanzapine, risperidone, ziprasidone) has not revealed any considerable differences between groups as regards the reduction of negative symptoms. Moreover, the meta-analysis of the results of two studies has demonstrated significant superiority of quetiapine [36], which has not, however, been confirmed by the study published in 2017 [56]. At the same time, no differences vs. ziprasidone have been confirmed by the study by Sacchetti et al. [57].

4.1.5. Quetiapine

The systematic review by Krause et al. [25] has revealed two studies comparing quetiapine to olanzapine [58, 59] and one comparing quetiapine and risperidone [60], all in the population with prominent negative symptoms. In comparison to olanzapine no statistically significant difference between groups has been observed, whereas compared to risperidone quetiapine has demonstrated a statistically significant advantage. Nevertheless, the comparison to risperidone is burdened with certain uncertainty due to the fact that, according to the study authors, the differences between groups in terms of the reduction of negative symptoms are statistically insignificant.

Other identified data pertain to the general population of schizophrenia subjects. The results of two meta-analyses [32, 33] including 6 and 5 studies, respectively, have not demonstrated statistically significant advantage of quetiapine over placebo. The results of the study by Kahn et al. [61] indicate, at the same time, that extended-release

quetiapine in large doses (600–800 mg daily) is more efficacious in treating negative symptoms than placebo is. The same study has not demonstrated such superiority for lower doses of extended-release quetiapine or standard-release quetiapine.

At the same time, the results of the meta-analysis by Leucht et al. [35] indicate that based on 10 studies it is impossible to conclude about statistically significant advantage of quetiapine over first-generation medications in reducing negative symptoms. The lack of statistically significant difference vs. chlorpromazine has been demonstrated in the study by Li et al. [62] published later. At the same time, a study including patients with the first episode of schizophrenia [63] has demonstrated a statistically significant advantage of quetiapine over haloperidol.

Just like in the case of a direct comparison between quetiapine and second-generation medications (olanzapine, risperidone, ziprasidone), no statistically significant differences in reducing negative symptoms have been revealed. Only the meta-analysis of the results of two studies has revealed a significant advantage of quetiapine over clozapine [36]. The results of more recent publications largely overlap with those presented in the above-mentioned studies. In studies with varied observation periods (from 6 to 52 weeks), no statistically significant differences between quetiapine and risperidone, olanzapine and aripiprazole [64–71] have been demonstrated. Moreover, the study by Kumar et al. [56] has also not revealed any differences vs. clozapine. Only one short-term study has demonstrated the advantage of quetiapine over risperidone [72]. The results of the comparison to paliperidone are ambiguous – the advantage of paliperidone was demonstrated after 14 days of the therapy, but after 42 days it was statistically significant for only one out of two statistical methods employed [73].

4.1.6. *Lurasidone*

The results of the systematic review by Krause et al. [25] have not identified any studies assessing the impact of lurasidone on the reduction of negative symptoms in the population of patients with predominant or prominent negative symptoms.

As regards the efficacy of lurasidone in treating negative symptoms in the general population of schizophrenia patients, the review by Fusar-Poli et al. [32] includes two studies comparing the agent to placebo. The study results are not consistent – one of them has demonstrated significant advantage of lurasidone, and the other one the lack of differences between groups. In two other studies comparing lurasidone vs. placebo in patients with illness exacerbation [74, 75], statistically significant advantage of lurasidone has been demonstrated for the 80 and 120 mg dose. In the study comparing the medication to risperidone in exacerbated patients [76], no statistically significant differences between groups have been revealed. For the comparison against quetiapine [77] no differences for groups of patients with illness exacerbation have been demonstrated. At the same time, the results of the comparison to ziprasidone are ambiguous, and depending on the statistical method used, there is either no difference between groups, or statistically significant advantage of lurasidone [78] is demonstrated.

4.1.7. Olanzapine

The systematic review by Krause et al. [25] has identified three studies assessing the impact of olanzapine on the reduction of negative symptoms in the population of patients with predominant negative symptoms [21, 52, 79] and 3 studies in the population of patients with prominent negative symptoms [58, 59, 80].

In the population with predominant negative symptoms the study results indicate that there are no statistically significant differences between olanzapine and amisulpride, asenapine, and an advantage over haloperidol has been demonstrated (according to the opinion of the review authors, the results of the comparison against haloperidol including a very small patient population require a further verification). The results of the comparison to placebo are ambiguous and – depending on the used method of data analysis and the dose – they demonstrate either no differences or superiority of olanzapine.

On the other hand, in the population of patients with prominent negative symptoms no differences vs. quetiapine and advantage of olanzapine over risperidone has been demonstrated. The authors of the comparison against risperidone indicate that both medications reduce negative symptoms, but the effect in the group of patients treated with olanzapine is more noticeable. The results of another study on the population of patients with prominent negative symptoms has demonstrated statistically significant advantage of olanzapine over risperidone in reducing negative symptoms and, at the same time, this difference is also significant as regards the reduction of positive symptoms, which might suggest potential impact of the improvement in this respect on results attained for negative symptoms [81].

The data for the subgroup of patients with prominent negative symptoms and for the population with the deficit syndrome have been isolated in the study by Tollefson et al. [82]. For both patient subgroups a statistically significant advantage over placebo and haloperidol has been demonstrated only for the highest of all three analyzed olanzapine doses.

The remaining identified trials pertain to the general population of schizophrenia patients. The review by Leucht et al. [33] has demonstrated significant superiority of olanzapine over placebo based on the meta-analysis of the results of 5 studies. It has been confirmed by the results of studies by Wang et al. [83], Schmidt et al. [84], Shen et al. [85]. On the other hand, for trials with observation period of 4 weeks only no significant differences between olanzapine and placebo [86–88] have been revealed.

The outcomes of two other trials with longer observation period are no longer that clear. The study by Hamilton et al. [89] has demonstrated statistically significant superiority of the highest of all three assessed doses of olanzapine over haloperidol in reducing negative symptoms, but at the same time, it has not been demonstrated for the comparison to placebo. Just like another trial [90], it has not managed to demonstrate significant difference in maintenance therapy vs. placebo in patients previously stabilized on olanzapine.

The results of the meta-analysis of 17 trials comparing olanzapine to first-generation drugs demonstrate its statistically significant superiority [35]. The outcomes of trials

published later or not included in the analysis are ambiguous. Several of them have demonstrated the superiority of olanzapine over haloperidol or first-generation drugs [91–94], while others have not demonstrated it [95–97]. What seems to be interesting in this context is the result of the study by Crespo-Facorro et al. [98] in which the superiority of olanzapine in reducing negative symptoms over haloperidol and risperidone for the population with the first schizophrenia episode has been demonstrated for the 12 month period, but once the results were adjusted taking account of confounding factors related to secondary negative symptoms, such as extrapyramidal and depressive symptoms, the differences between both groups were no longer statistically significant.

No differences for the comparison against risperidone can be confirmed by the results of the meta-analysis of 12 trials conducted within the review by Leucht et al. [36], which has not demonstrated statistically significant differences vs. other second-generation medications, namely amisulpride (4 trials), clozapine (6 trials), quetiapine (6 trials), and ziprasidone (2 trials). Numerous additional trials confirm the results of the aforementioned meta-analyses, not revealing any significant differences between olanzapine and other second-generation medications [46, 65, 68–70, 99–109]. But there are also some studies demonstrating superiority of olanzapine over risperidone and ziprasidone [110–112].

In spite of such rich evidence for olanzapine efficacy, differences in the assessed population and in research methods make the results slightly ambiguous.

4.1.8. Paliperidone

The review by Krause et al. [25] has not identified any trials assessing the impact of paliperidone on the reduction of negative symptoms in the population of patients with predominant negative symptoms or prominent negative symptoms.

The efficacy of extended-release paliperidone vs. placebo in reducing negative symptoms in patients with acute schizophrenia phase has been confirmed in several 6 week clinical trials [113–115]. Based on the data from the aforementioned trials it has been possible to isolate the results for the subpopulation of patients with predominant negative symptoms – it is noteworthy here that patients with predominant negative symptoms have been defined as ones with negative symptoms accounting for at least 40% of the maximum score on the PANSS scale (≥ 24 points), and positive symptoms for under 40% of the maximum score (< 27 points) – nevertheless, it needs to be stressed that those studies have not been designed to assess this particular subgroup of patients. The results of this analysis have demonstrated the superiority of paliperidone over placebo, both in the population of patients with and without predominant negative symptoms [116].

Other trials assessing the efficacy of paliperidone have been carried out on a total population of schizophrenia patients. Statistically significant superiority of paliperidone in reducing the severity of negative symptoms vs. placebo has been demonstrated in one short-term trial [117], while in the remaining two [118, 119], after the initial stage of stabilization of all patients taking paliperidone, no statistically significant difference vs. placebo was observed at further stages of the trial.

The results of the comparison to risperidone for observation periods from 12 to 26 weeks have not revealed any statistically significant differences in reduction of negative symptoms [120–123]. The results of the comparison to quetiapine are ambiguous [73]. The results of the comparison to olanzapine have not revealed any differences between groups [107], whereas in another study [124] the authors have pointed to no differences between those medications.

4.1.9. Risperidone

The review by Krause et al. [25] has identified one comparative trial of risperidone and cariprazine in the population of patients with predominant negative symptoms [50] as well as three studies comparing it to quetiapine, olanzapine and flupentixol [60, 80, 125] in the population of patients with prominent negative symptoms.

The comparison to cariprazine has demonstrated statistically significant superiority of the latter. The comparison to flupentixol has demonstrated nominal superiority of risperidone.

In the population with prominent negative symptoms, statistically significant superiority of quetiapine has been demonstrated (a similar result to this study has also been included in the review by Leucht et al. [36]). Nevertheless, the comparison to quetiapine is burdened with certain uncertainty because of the fact that according to the authors of the trial, the differences between groups in reducing negative symptoms are not statistically significant. The authors of the trial comparing risperidone to olanzapine have demonstrated that both medications reduce negative symptoms, but the effect in the group of patients treated with olanzapine is more visible. In another study on a population of patients with prominent negative symptoms, a statistically significant advantage of olanzapine over risperidone in reducing negative symptoms has been demonstrated and, at the same time, there has also been a significant difference in the reduction of positive symptoms, which might suggest potential impact of improvement in this respect on the results obtained for negative symptoms [81]. Even though the results of the comparative trial against cariprazine clearly demonstrate the superiority of cariprazine over risperidone, then the comparison against other medications for the population with negative symptoms is not free of limitations and its results need to be treated with caution.

Other identified scientific evidence pertains to the general population of schizophrenia patients in which also the impact of the medication on severity of negative symptoms has been explored. The review by Leucht et al. [33], based on the meta-analysis of 6 trials, has revealed statistically significant superiority of risperidone over placebo. Those results are confirmed by the studies by Casey et al. [126], Durgam et al. [127] and Nasser et al. (new risperidone formulation) [128] in which the superiority of risperidone over placebo has been demonstrated for the 6 and 8 week observation period.

The results of the meta-analysis of 30 trials comparing risperidone to first-generation medications have demonstrated its statistically significant superiority [35]. The results of trials published later or not included in the review reveal the lack of differences between first-generation drugs over the short period of time (6–8 weeks)

[129, 130], and statistically significant superiority of risperidone for the 12 month observation period [131, 132].

The results of meta-analyses for the comparison of risperidone to second-generation medications have not revealed any statistically significant differences vs. [36]: amisulpride (3 trials), aripiprazole (2 trials), clozapine (4 trials), olanzapine (12 trials), quetiapine (7 trials), sertindole (1 trial), ziprasidone (2 trials). These results are confirmed by the data coming from other publications. 13 short-term trials [42–46, 66, 105, 106, 120, 122, 123, 133, 134] have not demonstrated significant differences vs. olanzapine, quetiapine, aripiprazole, paliperidone and sertindole. At the same time, the results of 8 long-term studies have revealed differences in reduction of negative symptoms for the comparison of risperidone to ziprasidone, second-generation medications (taken into account as the general category), olanzapine, quetiapine, and paliperidone [69, 76, 101, 102, 121, 135–137]. Single trials have demonstrated the advantage of olanzapine for the 12 – and 52-week observation period [110, 111] or of quetiapine for the 12-week observation period [72]. The outcomes of the trial by Crespo-Facorro et al. [98] seem to be particularly interesting in this context, as they have demonstrated the superiority of olanzapine over haloperidol and risperidone in reducing negative symptoms in the population with first schizophrenia episode for the 12-month observation period, but once the results were adjusted taking account of confounding factors related to secondary negative symptoms, such as extrapyramidal and depressive symptoms, the differences between groups were no longer statistically significant.

4.1.10. Sertindole

The review by Krause et al. [25] has not identified any trials assessing the impact of sertindole on the reduction of negative symptoms in the population of patients with predominant negative symptoms or with prominent negative symptoms.

The identified trials have been carried out on the general population of schizophrenia patients, for which the impact of sertindole on the reduction of severity of negative symptoms has been evaluated. In the review by Leucht et al. [33], the meta-analysis of results of 4 trials has demonstrated statistically significant advantage of sertindole over placebo. At the same time, in the meta-analysis of the results of 4 studies comparing sertindole to first-generation medications, no statistically significant superiority of sertindole has been demonstrated [35]. The review of comparisons against second-generation medications, by Leucht et al., has identified only one trial that has not failed to demonstrate statistically significant difference against risperidone [36]. The results of three short-term trials published later have not revealed any statistically significant difference vs. risperidone and olanzapine [99, 103, 133].

4.1.11. Ziprasidone

The systematic review by Krause et al. [25] has identified one trial including the population with prominent negative symptoms, which has not demonstrated statistically significant difference between ziprasidone and amisulpride [31]. The remaining trials

assessing the efficacy of ziprasidone in reducing the severity of negative symptoms have been carried out on the general population of schizophrenia patients.

The results of a comparison against placebo presented in the meta-analysis of three trials have demonstrated a statistically significant advantage of ziprasidone [33]. For the short-term observation period of an additional study we can also observe the superiority of ziprasidone over placebo [138]. The comparison to first-generation drugs based on the results of three trials has not demonstrated any statistically significant differences between particular groups. The results of an additional study indicate that for the three year observation period, the differences vs. haloperidol are significant for a higher range of ziprasidone doses (80–160 mg), whereas for lower dose ranges (80–120 mg) the difference is of no statistical significance [139].

The data described in the review by Leucht et al. [36] indicate that there are no statistically significant differences vs. second-generation medications. The majority of trials published later confirm those conclusions for both short [48, 100, 104, 112] and long-term observation period [135] vs. risperidone.

4.2. Potentially efficacious medications with different mechanism of action

4.2.1. *Glutaminergic transmission*

Many agents affecting ionotropic and metabotropic receptors have been tested. In the majority of cases the obtained clinical results have not been satisfactory [13].

Glycine medications. In recent years, many agents stimulating glycine-binding sites on NMDA receptors [140, 141] have been studied. In initial trials, an improvement of both negative symptoms, and cognitive deficits were observed, but finally the results of those studies have failed to meet the assumed clinical goals [19].

Bitopertin (glycine reuptake inhibitor), in spite of wide-ranging phase III trials, the medication has finally not met the requirements that would allow for its market authorization [142].

Memantine. A study on a sample of 40 patients has demonstrated a considerable improvement in the therapy of primary negative symptoms with memantine in combination with risperidone [143]. Nevertheless, the meta-analysis of previous papers has not confirmed significant action of memantine [13].

4.2.2. *Central nervous system (CNS) stimulants*

The key success of trials conducted so far is the fact that CNS stimulants administered along with antipsychotics have not caused psychotic exacerbations [144]. Various large, properly designed trials are planned to be carried out for various active ingredients. At least one of them has already been successfully completed [145].

Lisdexamfetamine. The medication has been used to treat schizophrenia with predominant negative symptoms. An attempt to add lisdexamfetamine to antipsychotic therapy has turned out to be efficacious – the level of negative symptoms has been considerably reduced and, at the same time, creative symptoms have not

exacerbated. The discontinuation of Lisdexamfetamine therapy has not led to any adverse events [145].

Modafinil and armodafinil. The meta-analysis of 8 trials has revealed the benefits of treating negative symptoms with these medications, yet the effect as such was limited quantitatively [146].

4.2.3. Antidepressants

Adding antidepressants to antipsychotic therapy has been a common practice for a long time. Any possible mood enhancement is to reduce at least secondary negative symptoms. But there are few convincing, methodologically advanced papers that would confirm such concepts experimentally. In recent years, mostly catecholaminergic antidepressants have been tested in such combinations [13]. Neither the methodology nor the results of these trials have been clear [147]. What can encourage the use of antipsychotic and antidepressant combinations is the observed significant reduction of mortality among patients treated with them (HR: 0.57) [148].

4.2.4. Immunomodulatory medications. Anti-inflammatory medications

The action of some immunomodulatory and anti-inflammatory medications has also been observed in relation to the inflammatory theory in the etiopathogenesis of schizophrenia.

Minocycline. Six trials comparing the combination of minocycline with antipsychotics against placebo have been carried out [149]. In the meta-analysis of those trials the improvement of negative symptoms and no differences vs. placebo as regards positive symptoms have been demonstrated. Minocycline influences the regulation of the synapse remodeling process during late adolescence, when patients often fall ill with schizophrenia and negative symptoms start developing [150]. Further trials are necessary.

Celecoxib. In a host of studies, favorable results of combining celecoxib with antipsychotics in reducing both positive and negative symptoms have been demonstrated [151]. The combination of celecoxib and amisulpride allows for achieving far deeper reduction of negative symptoms than amisulpride in monotherapy. The use of anti-inflammatory medications was the most effective at the initial stage of schizophrenia.

4.2.5. Omega-3 acids

According to the NICE analysis, omega-3 acids virtually do not have any impact on the course of schizophrenia [22]. Out of eight placebo-controlled, randomized trials, in 4 no difference has been demonstrated, and in the remaining 4 only 'minimal changes', of no clinical significance.

Recapitulation

The existing recommendations do not give a definite answer to the question about the treatment of negative symptoms of schizophrenia, therefore it is necessary to create appropriate recommendations.

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