

Polish Psychiatric Association working group consensus statement on non-pharmacological methods in the treatment of negative symptoms of schizophrenia

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Summary

This consensus statement has been prepared by a group of experts consisting of professionals with long experience in the treatment of psychiatric disorders, who were appointed by the Management Board of the Polish Psychiatric Association. The evaluation involved the analysis of literature databases and information derived from meta-analyses of these data for years 2010–2020. The searched publications were in English, German and Polish language versions and involved interventions performed in groups of adult patients. The efficacy of non-pharmacological methods applied for treatment of negative symptoms of schizophrenia were compared with effects of a different treatment/combined treatment/a group with no intervention.

When formulating the recommendations, the experts analyzed the source data in terms of their application in the Polish conditions. The current recommendations of academic societies and literature on the treatment of schizophrenia with predominant negative symptoms were taken into account. The experts included items that involved a comparison of a study group in terms of non-pharmacological interventions, and pharmacologically treated cases were taken into account only when divisions were made into standard treatment and additional intervention. The results were divided into 7 sections: 1. Psychoeducation, 2. Psychotherapy (individual, group and family therapy), 3. Psychiatric rehabilitation, 4. Emotional intelligence, social skills and mindfulness training, 5. Cognitive remediation/rehabilitation, cognitive train-

ing, 6. Clinical efficacy of physical activity, behavioral activation and metacognitive training, 7. Other rehabilitation methods (including biological methods).

The recommendations were debated by experts, approved by the Management Board of the Polish Psychiatric Association, and – upon consideration of the submitted comments – adopted as a consensus statement of the Association with the recommendation of their application in the treatment of schizophrenic patients in Poland.

Key words: schizophrenias, negative symptoms, non-pharmacological treatment

Introduction

Because of their nature, negative symptoms of schizophrenia have an exceptionally severe impact on daily functioning of patients and are a significant burden for patient's immediate environment and healthcare system [1]. A particularly affected group includes patients whose negative symptoms are persistent and predominant [2]. The available epidemiological data on the prevalence of negative symptoms are diverse and limited. Primary persistent negative symptoms develop in 25–30% of patients, and Polish studies report that the number of patients with these symptoms reaches approximately 20 thousand [1]. Depending on the adopted definition, it is estimated that these symptoms persist in 20–40% of patients with the first schizophrenic episode.

The classical set of negative symptoms includes:

- diminished emotional expressiveness (flattened or blunted affect, with resulting 'facial masking');
- inability to experience pleasure (anhedonia);
- poverty of speech, both in terms of used vocabulary and conveyed messages (alogia);
- decreased social needs, isolation from other people;
- lack of will to strive for something (avolition) [3].

The therapy of patients with negative symptoms is difficult, comprehensive and requires accurate identification of the target patient group and planning of the individualized treatment process, comprising both pharmacological interventions and other methods, including psychosocial approaches.

An adequately selected pharmacological therapy with antipsychotic medications continues to remain the basic short – and long-term method to manage schizophrenia and prevent illness recurrences [4]. It is therefore practically impossible to evaluate non-pharmacological methods in the treatment of negative symptoms of schizophrenia in isolation of concomitant pharmacotherapy. It is not the intention of the authors of this review to claim that pharmacotherapy is superior to non-pharmacological approaches, or to promote a strictly biological approach to schizophrenia treatment. The intention is rather to simply state the fact that non-pharmacological methods may and should be used concurrently with an individually selected antipsychotic drug(s).

Basically all antipsychotic medications are dopamine D2 receptor antagonists with features of a neuroleptic, i.e., of an agent that – in appropriately large doses – does elicit emotional indifference and psychomotor retardation. Unfortunately, these neuroleptic effects of antipsychotics may intensify negative (deficit) symptoms of schizophrenia [4, 5]. Moreover, some antipsychotics have a potent effect on other neurotransmission systems. It is therefore possible that additional receptor effects of an antipsychotic, e.g., antihistaminic or cholinolytic effects, will lead to sedation and cognitive disorders that will intensify the negative symptoms of the illness [6]. This means that, in practice, non-pharmacological therapeutic interventions may also (or in some cases, mainly) affect secondary negative symptoms induced by antipsychotic treatment. Prior to the implementation of non-pharmacological methods in the management of negative symptoms, it would be important to ensure that the deficit symptoms are primary and cannot be eliminated by dose modification or by changing the antipsychotic.

Attention should be drawn to the group of dopamine receptor partial agonists: aripiprazole, brexpiprazole and cariprazine. By contrast with typical antagonists, these agents do not block dopaminergic signals in a zero-to-one manner. Moreover, cariprazine is preferential towards dopamine D3 receptors that are functionally linked with the emotional and motivational spheres in the limbic system and cerebral cortex. Partial agonism towards D3 receptors located in the limbic system and frontal cortex may translate to additional antidepressant effects and limit negative symptoms of schizophrenia. Cariprazine is also a partial agonist of serotonin 5-HT_{1A} receptors, and their stimulation is linked with antidepressant effects of SSRI drugs [7]. Cariprazine is the only second-generation antipsychotic for which statistically significant superiority over another second-generation drug (risperidone) has been confirmed in a study among patients with predominant negative symptoms with this clinical condition remaining stable for at least 6 months [8].

The above considerations lead to a conclusion that results from clinical trials should be properly interpreted. Concomitant or even previous pharmacotherapy might have significantly affected the results of a given efficacy trial evaluating a non-pharmacological intervention in the treatment of negative symptoms. The standards for pharmacotherapy in schizophrenia with negative symptoms, created by the expert panel from the Management Board of the Polish Psychiatric Association (PPA), distinguish two patient populations with negative symptoms: patients with the full spectrum of schizophrenia symptoms, in whom practically any of the second-generation antipsychotics can be selected, and patients with predominant and persistent negative symptoms, who are recommended cariprazine [9]. On the other hand, it seems that a breakthrough in the therapy of deficit schizophrenia symptoms cannot be expected to occur without development and broader implementation of non-pharmacological methods [6, 10].

Aim and method

When creating these recommendations, the working group, which consisted of the members of the board and experts of the Polish Psychiatry Association as well as the national consultant for adult psychiatry, took into account the review of the literature from 2010–2020:

- publications in English, German and Polish;
- interventions in groups of adult patients;
- the efficacy of non-pharmacological interventions in the treatment of negative symptoms of schizophrenia were compared with the effects of a different treatment/combined treatment/a group with no such interventions.

The leading academic databases (Medline – PubMed access, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, and Cochrane Central Register of Controlled Trials) were searched for original clinical trials on non-pharmacological treatment approaches in schizophrenic patients.

The original clinical trial search and subsequent selection of publications based on titles, abstracts and full texts, resulted in a significant number of found clinical trials on non-pharmacological interventions in schizophrenia treatment.

The following were included in this review:

- trials with only schizophrenic patients or mixed patient populations with schizophrenia and schizophrenia spectrum disorders;
- trials with the primary aim to evaluate the efficacy of non-pharmacological methods in the treatment of schizophrenia.

The following studies were excluded:

- trials with the aim to evaluate/compare various scales/methods used to assess the efficacy of applied treatment methods;
- trials with the primary aim to evaluate the effects of applied therapy on patient's family burden and condition;
- trials regarding response predictors, cost analyses and mechanisms of action of applied therapies;
- trials with healthy volunteers as controls;
- trials that were secondary analyses conducted on the basis of results from primary studies.

Key words: Schizophrenia OR schizophrenias OR schizophrenic disorders OR schizophrenic disorder OR dementia praecox OR dementia precox OR schizophrenic syndrome AND psychotherapy OR psychotherapies OR psychotherapists OR psychotherapist OR clinical psychotherapists OR clinical psychotherapist OR psychotherapeu-

tic processes OR psychotherapeutic training; group psychotherapy OR group therapy OR group psychotherapy OR group treatment OR community therapy OR community treatment; family therapy OR family intervention OR family psychiatry OR family psychotherapy OR family treatment OR vector therapy; individual therapy.

The search of the basic academic databases (Medline, Embase and Cochrane Library) resulted in the identification and description of: 43 therapies of 401 randomized trials.

The following were identified:

- 16 randomized trials (cited in 17 references and published within the past 10 years) on psychoeducation;
- 11 randomized trials (cited in 12 references and published within the past 10 years) on psychotherapy (individual, family, community therapy);
- 24 randomized trials (published within the past 10 years) on social and professional rehabilitation (19 and 5 trials, respectively);
- 7 randomized trials on various forms of training/therapy aiming to reinforce emotional intelligence;
- 73 randomized trials (published within the past 10 years) on various forms of cognitive remediation/rehabilitation/therapy;
- 37 randomized trials and 2 observational studies on TMS;
- 2 randomized trials and 1 case report on executive function training;
- 23 randomized trials (cited in 24 references) on various forms of physical activity;
- 20 randomized trials (cited in 21 references) and 1 observational study on metacognitive training (MCT);
- 2 observational studies on light therapy;
- 3 randomized trials, 1 observational study and 1 case report on EEG biofeedback/neurofeedback (BF/NF) training;
- 4 randomized trials and 2 observational studies on virtual reality;
- 1 randomized study concerning a mobile application;
- 1 study (consolidating the results from 2 observational studies) on using wearables;
- 9 RCTs on the application of various combined interventions applied in the treatment of schizophrenia/schizophrenia spectrum disorders, which cannot be categorized into a single group of the aforementioned studies.

The trials were divided into 7 sections: 1. Psychoeducation, 2. Psychotherapy (individual, group and family therapy), 3. Psychiatric rehabilitation, 4. Emotional intelligence, social skills and mindfulness training, 5. Cognitive remediation/rehabilitation, cognitive training, 6. Clinical efficacy of physical activity, behavioral activation and metacognitive training, 7. Other rehabilitation methods (including biological methods).

The recommendations were created on the basis of presentations prepared and presented by experts during working meetings that were conducted online since November 2020 to February 2021.

When formulating recommendations for non-pharmacological management in schizophrenic patients with negative symptoms, with the indication of the class of recommendation and level of evidence (Table 1), the experts analyzed source recommendations in terms of their application to the Polish conditions.

Table 1. Interventions used in the treatment of schizophrenia with negative symptoms with evaluation of the class of recommendation and level of evidence that confirm their efficacy

Intervention	Publications describing the recommended protocols for interventions	Class of recommendation and level of evidence	Remarks
Psychoeducation	[16–18]	level of evidence: B class of recommendation: IIb	1 RCT on family psychoeducation (patient plus family and several sessions without the patient), other studies indicating efficacy in the therapy of negative symptoms: studies in combination with social skills training or studies with mindfulness training
Individual, group and family psychotherapy	[27, 28]	level of evidence: B class of recommendation: IIa	1 RCT on family psychotherapy and the effects of group psychotherapy in combination with cognitive rehabilitation showed improvement in negative symptoms of schizophrenia
Psychiatric rehabilitation	[38–40]	level of evidence: A class of recommendation: IIa	24 RCTs. The best outcomes (reduction in the severity of psychiatric symptoms, improved general performance, the longest work duration, the highest employment rates) relate to patients who enter the program of integrated supported employment.
Emotional intelligence (EI) training	[35–39]	level of evidence: B class of recommendation: IIb	7 RCTs, not all results were statistically significant, limitations also included too small sample sizes
Social skills training (SST)	[15, 17, 39, 41, 42]	level of evidence: B class of recommendation: IIa	3 studies, including one RCT, confirm efficacy, while 6 studies do not confirm efficacy. In the early stage of schizophrenia, combining pharmacotherapy with SST lowers treatment discontinuation rates

table continued on the next page

Mindfulness training	[43–47]	level of evidence: B class of recommendation: IIb	6 RCTs: improvement in terms of illness insight, symptom severity, frequency and duration of hospitalization; restricted group representativeness
Cognitive remediation or cognitive training	[56–61]	level of evidence: B class of recommendation: IIa	Numerous RCTs, also in multicentre settings, evaluating mainly improvement in cognitive functions; less evidence for the efficacy in negative symptoms of schizophrenia
Physical activity	[62–65, 67]	level of evidence: B class of recommendation: IIb	23 RCTs, mainly single-centre studies with small sample sizes. Physical activity is a valuable form of therapy in schizophrenia. Being supplemental to pharmacotherapy, it may lead to the reduction of the severity of negative symptoms and facilitate the improvement of patient functioning and their quality of life
Repetitive transcranial magnetic stimulation (rTMS)	[74]	level of evidence: B class of recommendation: IIb	A dozen or so sham-controlled RCTs with mostly positive results. One negative multicentre study

EBM – evidence-based medicine; Classes of recommendation: I – evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective (treatment is recommended); II – conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure; IIa – weight of evidence/opinion is in favor of usefulness/efficacy (treatment should be considered); IIb – usefulness/efficacy is less well-established by evidence/opinion (treatment may be considered); III – evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful (treatment is not recommended). Levels of evidence: A – data derived from multiple randomized clinical trials or meta-analyses; B – data derived from a single randomized clinical trial or large non-randomized studies; C – consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Psychoeducation

Psychoeducation is a group therapy where, on the one hand, the therapist provides information about a disease (etiology, symptoms, treatment, etc.) and, on the other hand, participants exchange their own experiences and provide support to one another [11]. This method was first described by Carol M. Anderson in 1980s as a behavioral therapeutic intervention aiming to inform patients about their disease and train communication skills, problem-solving and assertiveness [12].

Most of the analyzed studies on the effect of psychoeducational (and mixed) interventions on the course of schizophrenia involved the evaluation of different variables, such as illness awareness, insight, indices of rehospitalization and treatment

cooperation as well as illness symptoms, including negative symptoms. Unfortunately, these interventions lack homogeneity. Some were assessed in combination with social skills training, others were based on mindfulness-based intervention (MBI) or involved the patient's family (with or without patients), and not all were performed in a randomized setting.

Several studies evaluated symptoms using the PANSS total score (without any division into subscales or with a change in the negative symptom subscale being statistically insignificant). Two trials detected significant differences between the groups that used classical psychoeducation, MBI and standard therapy [13, 14]. Mindfulness-based psychoeducation was found to be the most effective in terms of psychotic symptoms, but the results of a *post hoc* analysis for negative subscales were not reported [14]. In one trial [15], where family psychoeducation was combined with social skills training, a statistical effect of the group and time was observed for the psychoeducation group compared with the customary treatment group, but ultimately there were no statistically significant differences between the evaluated methods (the authors' conclusion).

In the references, there was one randomized clinical trial (RCT) to evaluate the efficacy of family psychoeducation compared with standard treatment. Significant superiority was observed for the evaluated intervention in the period of a 12-month follow-up [16]. The family psychoeducation program involved several separate meetings with three to four families of patients, conducted by two family therapists, followed by several meetings with all families without the patient and further several meetings with all families and patients.

Moreover, the effects of combined therapy were also evaluated in an RCT [17]. In this case, family psychoeducation and social skills training were applied. Based on the PANSS and PANSS positive and negative subscales, the intervention was found to be more effective than customary treatment. The period of observation and training reached 12 months.

Another RCT evaluated mindfulness training, and involved more yoga and meditation than psychoeducation as such. This was found to be more effective for the management of negative symptoms than customary treatment; SANS score improvement was observed after 8 weeks, but not after 3 months [18].

An interesting study was conducted in Poland, where two interventions were compared: after the first psychiatric hospitalization, controls remained under individual care, while the study group patients entered the community treatment program and were referred to a day-care ward and community-based group therapy, such as psychoeducation, group psychotherapy, therapeutic camps or hostel. Families attended group psychoeducation for families, and subsequently joined a common group with patients. Different variables were assessed, including negative syndrome severity in the BPRS. In the study group, the severity of negative symptoms decreased during

their participation in the program and then intensified after twelve years without reaching the level from the index hospitalization. The dynamics of the negative syndrome was similar in the control group; the severity was generally greater, but there were no statistically significant differences [19].

This review indicates that most studies evaluate the effect of combined interventions on different variables, including negative symptoms. It is therefore difficult to sum up and formulate explicit conclusions regarding the therapy of negative symptoms of schizophrenia from studies on the efficacy of psychoeducation as such.

Based on the available evidence on the efficacy of psychoeducation in the treatment of negative symptoms of schizophrenia, the indicated class of recommendation is IIb (may be considered), while the level of evidence is B. This means that there is conflicting evidence and/or discrepant opinions regarding the efficacy of the procedure, and relevant data are derived mainly from 1 RCT in terms of family psychoeducation (patient plus family and several sessions with the patient) where evaluation of negative symptoms was the primary objective [16], from the study in combination with social skills training [17] or from the study with mindfulness training [18].

Individual, group and family psychotherapy

The clinical practice demonstrates that the addition of non-biological therapies to pharmacotherapy in schizophrenic patients is reasonable. The first form of psychotherapy that received broad approval and was recommended in APA and NICE guidelines was cognitive behavioral therapy (CBT) [20]. However, most studies were focused on positive symptoms and relapse prevention, while negative symptoms received less attention.

A meta-analysis of 72 studies on the effects of psychological and psychosocial interventions on the severity of negative symptoms of schizophrenia was published in 2017 [21]. Twenty-six publications evaluated the efficacy of cognitive behavioral therapy in the treatment of psychosis, and two of these concerned CBT adjusted to the needs of patients with negative symptoms. A positive effect was seen when compared to treatment as usual (TAU) CBT, both at the end of therapy and in long-term follow-up (a mean of 27 months). There were no differences in the effects of psychotherapy on negative symptoms in patients with early illness compared to those with late illness (under and over 35 years of age). Group therapy was not significantly different in terms of efficacy in negative symptoms than individual therapy, but interventions that lasted longer than 45 minutes per week were markedly superior. A greater positive effect was demonstrated with higher baseline severity of negative symptoms.

Other authors have shown that group occupational therapy was associated with significant improvement in negative symptoms [22–25]. Nevertheless, a repeated evaluation of positive effects of the therapy revealed that they had not persisted over a longer period of time [26].

In a meta-analysis conducted by Lutgens et al. [21], family therapy was evaluated as a form of group therapy and single-family therapy, but no efficacy advantage was demonstrated compared to TAU. Moreover, Cai et al. [27], who enrolled more than 100 patients to their study, failed to show the efficacy of family psychotherapy on the severity of all symptoms in general and negative symptoms compared to TAU. Dyck et al. [16] drew contrasting conclusions after a one-year follow-up of 63 patients; they demonstrated that multiple-family psychoeducation-based therapy is more effective than TAU in terms of negative symptoms. They pointed to several potential mechanisms favoring negative symptom reduction. A therapeutic group enriches the patient and their family by providing them with experiences of similar families; it has a socializing value, which is enriching and stimulating, while negative symptoms are more pronounced in a non-stimulating environment. Family attitudes are improved, criticism is reduced, clear communication appears with realistic judgement concerning possibilities and limitations. Therapy decreases expressed emotion in the primary caregiver [28], while comprehensive family therapy helps improve patient's cognitive performance [27].

To sum up, group forms of psychotherapy seem to be the most effective in relieving negative symptoms of schizophrenia. All studies reported a decreased severity of negative symptoms after the applied therapy, even if the differences were not statistically significant when compared to controls. It must be remembered that therapeutic success of any psychotherapy is linked with participation, motivation and communication, which, by definition, makes treatment more difficult in patients with negative symptoms. The data on the efficacy of therapeutic interventions must be considered in the context of pharmacotherapy (e.g., adverse reactions, drug-related depression) and social position deterioration. It seems that the use of psychotherapy as auxiliary treatment of schizophrenia may bring benefits to patients with negative symptoms. To conclude, most research evidence supports the efficacy of psychotherapy in the treatment of negative symptoms of schizophrenia (class of recommendation IIa – should be considered, level of evidence B).

Psychiatric rehabilitation

Psychiatric rehabilitation is a system of coordinated community, psychological, educational, and medical interventions to help patients with mental disorders to function independently and to facilitate community integration. Its goal is to compensate for or eliminate functional deficits with interpersonal and environmental barriers that are linked with social disability. It also aims to restore the ability of independent living, facilitate socialization and conscious management of one's own functioning. Psychiatric rehabilitation involves medical, vocational and social measures. It is recommended that rehabilitation interventions should be available for patients in various institutions and facilities and that they should involve every stage of treatment.

The basic forms of rehabilitation are: skills trainings, psychoeducation, psychotherapy, music therapy, physical rehabilitation, and therapeutic camps. Psychiatry Day Wards or Psychiatric Rehabilitation Wards are examples of community-based interventions for schizophrenic patients. These wards employ training modules created by the Clinic Research Center for Schizophrenia and Psychiatric Rehabilitation of the University of California, which include: difficult interpersonal problem-solving activities, basic communication skills training, appearance and personal hygiene training, cooking training, financial training, technical training, practical skills training, social skills training, and training regarding active participation in pharmacotherapy [29]. These patients frequently manifest various cognitive deficits. Psychoeducation is a series of lectures about schizophrenia, its treatment and relapse prevention. It may be addressed to both the patient and his or her immediate family members [30]. The recommended psychotherapeutic program for patients after the first episode of psychosis involves individual short-term cognitive behavioral therapy, referred to as the “STOPP” program. The program involves the management of persistent positive symptoms that continue to occur despite pharmacological treatment. It consists of four phases: developing a therapeutic relationship; exploring psychosis and coping styles; developing the capacity to apply the knowledge to understand one’s experiences and feelings (insight); and finishing cooperation [31]. Vocational interventions conducted as part of employment support programs are also an important element of rehabilitation. These interventions involve employment support centers that offer help in finding a job, provide a career diagnosis and offer workshops and projects that facilitate employment.

The results of studies conducted among schizophrenic patients indicate that the patients who finished the program were characterized by significantly higher self-esteem, lower hostility levels and greater confidence in oneself and other people. They also had better insight in the motives of their own and other people’s behaviors, felt a greater need to care for others, cooperate and establish close interpersonal relationships, were more tolerant and spontaneous, and were characterized by better ability to adjust to a changing situation [31]. The studies on aerobic exercise in schizophrenic patients showed a significant effect on positive and negative symptoms and on cognitive performance [33]. To conclude, psychiatric rehabilitation is the most thoroughly explored intervention in terms of efficacy in negative symptoms of schizophrenia (level of evidence A); it should be considered in the treatment of patients with negative symptoms (class of recommendation IIa).

Emotional intelligence, social skills and mindfulness training

There is increasing evidence that negative symptoms of schizophrenia can be reduced by applying special, non-pharmacological intervention programs. The aim of this so-called training of cognitive learning in schizophrenia is to acquire new developmental and rehabilitational skills. The assumption is that they will improve “social

functioning of the brain” and preserve “social orientation”, eliminate the deficit effects of psychosis, and reduce the risk of developing an illness and recurrence [34]. One of the methods that is important for development and rehabilitation of schizophrenic patients is the use of training programs to improve emotional intelligence. It is believed that emotional intelligence (EI) plays a significant role in the manner in which an individual copes with their own and other people’s emotions on an everyday basis and is important with respect to individual mental health. Evidence suggests that EI training and development are feasible. EI training involves social self-perception and social perception of others, capability of emotional perspective changing, recognizing goals of other people’s actions, coping with negative emotions, such as anxiety, depression or aggression, and strengthening the ability to intensify positive emotions and to preserve them for a long period of time. EI training programs are based on diagnosed deficits within emotional perception and processing. Impaired understanding and regulation of emotions in daily activities of schizophrenic patients are associated with different aspects of their social functioning. Abnormal emotional expression in schizophrenia and limitations in revealing positive emotions are linked with cognitive deficits. Patients with a low level of emotional intelligence processes demonstrated worse psychosocial adaptation and did not react to environmental stimuli correctly, which hindered their ability to adjust to independent living and caring for oneself, even in the aspect of one’s own appearance and personal hygiene. The EI training is intended to be centered upon these fundamental processes in order to increase – in conjunction with modern antipsychotic treatment – the rehabilitational potential and quality of life of patients, especially those with predominant negative symptoms of psychosis [35]. The investigations regarding the clinical efficacy of emotional intelligence training identified 7 randomized trials on various forms of training aiming to reinforce emotional intelligence. It was observed that although emotion and theory of mind imitation training does not have an effect on emotional processing skills, it does significantly improve theory of mind skills. Patients subjected to this training had improved social cognition components, such as cognitive components and empathy. Social functioning improved as well [36–38]. It was also found that the severity of negative symptoms reduced upon therapy conclusion relative to the baseline status [39]. The effect of EI training on the severity of negative symptoms in the course of schizophrenia was not statistically significant when compared with controls. Low sample sizes were an important limitation for the results of the individual studies. To sum up, EI training in a schizophrenic patient with predominant negative symptoms may be considered, but studies have provided slightly less evidence to confirm the efficacy of this method (class of recommendation IIb, level of evidence B).

The combination of pharmacotherapy with psychosocial intervention in early stage of schizophrenia results in lower treatment discontinuation or treatment change rates, lower risk of relapse, better insight, improved quality of life, and better social

functioning than pharmacotherapy alone [40]. When considering the efficacy of psychosocial training, the following basic modules are included: patient and patient family education regarding basic psychiatric knowledge; independent living skills training (self-care, individual behavioral norms, shopping, entertainment); social skills training and vocational rehabilitation with behavioral intervention; cognitive intervention regarding mood and behavior modification by self-analysis and discovery of own problems [41]. Social skills training (SST) is used as one of social rehabilitation forms in schizophrenic patients with the aim to improve social functioning by experiencing feelings and building behavioral memory associated with being in social situations, broadening the range of executive skills and developing communication skills. The aim of SST in schizophrenia is also to prevent social withdrawal, develop skills to manage one's own emotions, express emotions or adequately react to emotions of other people. A positive effect of social skills training improves functioning in the family, among friends or at work. By using socially significant stimuli, SST is said to improve the processing speed and processing accuracy in the cerebral systems that are responsible for social input processing by means of exercises that are jointly centered on the perception of visual and auditory affect, perception of social signals, theory of mind, self-reference style and empathy [39]. Two studies evaluating SST efficacy revealed improvement in terms of psychopathology, discomfort and social cognition, social withdrawal, interpersonal communication and quality of life compared to groups receiving the standard of care. In addition, it was observed that the obtained positive results regarding negative symptoms and social discomfort persisted in a 6-month follow-up period. This confirms the efficacy of social skills training in outpatient therapy in schizophrenia [15, 17, 42]. As the results of the available studies mostly support the usefulness of this method, its application should be pragmatically considered (class of recommendation IIa, level of evidence B).

Mindfulness training holds an important position among psychological therapies that are said to help patients with schizophrenia. The mindfulness-based psychoeducation program (MBPP) defines mindfulness as a state of consciousness resulting from intentional direction of attention to what is being experienced at a given moment, without making any judgements. Mindfulness training requires intentional observations and calm, non-judgemental and accepting investigation into one's own experiences [43]. By means of mindful training and exercises, a schizophrenic patient may learn how to accept their own thoughts and feelings, and how to constructively regulate cognitive and emotional dysfunctions as well as behavioral manifestations. The application of mindfulness training in schizophrenia is justified by the course of psychosis with persisting abnormal perception or disorders of perception and thinking. Despite implemented pharmacological therapy, patients still experience residue psychotic symptoms that make them behave in an odd manner and may exacerbate anxiety, emotional disorders and disability. Patients defend themselves from the

discomfort of psychosis by adopting distraction, avoidance and suppression strategies. Nevertheless, the avoidance-based attitude potentiates distress and anxiety. This is strongly correlated with the risk of relapse and re-hospitalization. It has been noted that mindfulness training helps schizophrenic patients by letting them assume a more adaptive strategy of controlling and coping with psychotic symptoms and by reinforcing the ability to accept and tolerate negative thoughts and emotions [44, 45]. Mindfulness training teaches one to acknowledge and perceive input clearly, without emotions and without filtering it through earlier views. Its aim is to reach emotional balance, learn how to concentrate and relax, cope with stress, lower tension and develop skills to calm down. The search identified 6 randomized trials on the efficacy of mindfulness-based psychoeducation program in comparison to the standard of care. These programs encompassed: involvement in treatment and focusing on the awareness at a given moment; mindfulness in daily living and solving problems of daily living; mindfulness in the attitude to cope with difficulties resulting from the illness symptoms; and formulating plans to prevent recurrences and lead a mindful life [46, 47]. Compared with patients receiving the standard of care, those following the mindfulness-based psychoeducation program demonstrated markedly greater improvement in terms of illness insight, severity of symptoms, functioning as well as number and duration of re-hospitalizations. Although representativeness of the study group restricted to the Chinese population was a certain limitation of these studies, it seems that mindfulness-based psychoeducation program (MBPP) supports other therapeutic interventions, improves social functioning and is a justifiable option to prevent schizophrenia relapses. Considering the opinions supporting the usefulness and efficacy of this method in the program of comprehensive schizophrenia management, the said method cannot be overlooked (class of recommendation IIa, level of evidence B).

Cognitive remediation/rehabilitation, cognitive training

Cognitive remediation in schizophrenia was officially defined relatively recently – in 2010, by the Cognitive Remediation Experts Workshop as a behavioral training aiming to provide generalized and lasting improvement of cognitive processes (e.g., attention, memory, executive functions, social cognition, and metacognition) [48]. The pertinent literature also suggests that the term ‘cognitive remediation’ encompasses evidence-based so-called non-pharmacological methods to reduce cognitive deficits in schizophrenia, which may be understood in a ‘narrow’ way (as a set of cognitive exercises or interventions aiming to improve cognitive performance) or in a ‘broad’ way (as learning the skills to improve cognitive functions in order to reduce identified deficits) [46]. Furthermore, two main strategies have been distinguished within cognitive remediation: a compensatory strategy that consists in reducing the cognitive deficit by using other preserved cognitive functions or environmental resources, and

a restorative strategy that consists in reducing the cognitive deficit by improving the functioning of a specific cerebral system using neuroplasticity processes [50]. Two meta-analyses have also demonstrated a positive effect on psychopathological symptoms with low or moderate effect size, in particular with respect to the reduction of negative symptoms of schizophrenia [51, 52].

Negative symptoms frequently contribute to worse social functioning (e.g., in the family or work environments) and, in the long perspective, make recovery more difficult [53]. It has been shown that these symptoms are associated with cognitive functions, including cognitive resources, ability to use cognitive strategies, speed of reactions to stimuli, conceptual thinking, working memory, and executive functions [54, 55]. That is why the use of cognitive remediation methods as techniques of non-pharmacological intervention may be conducive to reduction of negative symptoms of schizophrenia. The literature suggests several neuropsychological mechanisms to elucidate this positive effect, which assumes an indirect form, meaning that cognitive remediation reduces cognitive deficits, and they mediate negative symptom reduction. The first mechanism is the impact of working memory; it is based on the fact that decreased working memory makes it difficult to represent and reach previous positive experiences, which diminishes patient motivation. The second mechanism is the impact of sensitivity to positive feedback; it consists in the fact that difficulties associated with using positive feedback to modify behavior by schizophrenic patients consolidate negative symptoms. The third mechanism is the impact of executive functions; it is manifested in the fact that difficulties in planning and fulfilling complex cognitive tasks induce withdrawal from activity and diminish motivation. The last mechanism is based on the impact of self-esteem; it is based on the fact that cognitive problems determine lower self-esteem which, in turn, causes patient withdrawal and diminished motivation [51].

In the current systematic review, 73 randomized trials were ultimately identified. These studies were published after 2010 and concerned the efficacy of various cognitive remediation techniques as a method of non-pharmacological treatment of schizophrenia. Based on the data presented in referential publications on the effect of the applied interventions on changes in negative symptoms in the PANSS or SANS scales, a statistically significant improvement in terms of the severity of negative symptoms was reported as a result of applying:

- cognitive remediation versus treatment as usual (TAU) ($p = 0.026$) [56];
- cognitive remediation versus occupational therapy with treatment as usual ($p = 0.03$) [57];
- cognitive remediation versus support group therapy ($p = 0.000$) [58];
- cognitive rehabilitation versus treatment as usual ($p = 0.001$) [59];
- cognitive and social interaction training versus social stimulation ($p < 0.001$) [60];
- integrated neurocognitive therapy versus treatment as usual ($p < 0.01$) [61].

To conclude, computer-aided cognitive rehabilitation, including so-called cognitive remediation or cognitive training, is an effective and patient-accepted method to treat cognitive deficits in schizophrenia or schizoaffective disorder; they offer improvement, restoration or compensation for impaired cognitive functions, thus improving patient daily functioning. However, the evidence for efficacy of cognitive remediation in the treatment of negative symptoms of schizophrenia is not as robust as with cognitive rehabilitation. The evidence confirming its validity was assessed as class of recommendation IIa (should be considered) with level of evidence B.

Physical activity, behavioral activation and metacognitive training

Various forms of physical activity are used as non-pharmacological therapy methods for managing negative symptoms of schizophrenia. Most randomized clinical studies on the clinical efficacy of physical activity involved analyses of relatively low sample sizes, and follow-up periods were not longer than 6 months.

If the physical activity program involves adequately selected aerobic exercises, it may effectively supplement standard pharmacotherapy and contribute to the reduction in the severity of negative symptoms [62, 63]. Analogous efficacy has also been demonstrated in exercise programs involving stretching, relaxation and treadmill march. Moreover, it has been observed that aerobic exercises are characterized by greater efficacy in relieving negative symptoms of schizophrenia than Tai-chi [64]. Yoga is also effective in relieving negative symptoms of schizophrenia. Several studies found that yoga brought a more lasting reduction of the severity of negative symptoms. However, one of these studies demonstrated that the effects were transient, and the efficacy was seen only directly upon conclusion of the intervention [65]. Other studies have shown that resistance exercises may also be a form of negative symptom-relieving therapy [66]. Also, a simple therapy involving walking occurred to be effective in terms of lowering the severity of negative symptoms, improving performance and improving quality of life in schizophrenic patients [67].

To sum up, physical activity is a valuable form of therapy in schizophrenia. Being supplemental to pharmacotherapy, it may lead to the reduction of the severity of negative symptoms and facilitate the improvement of patient functioning and their quality of life. The evidence for its efficacy is assessed as class of recommendation IIb and level of evidence B.

Behavioral activation is a therapeutic option in depression with scientifically proven efficacy. It has therefore been deduced that it could also prove effective in the therapy of negative symptoms of schizophrenia, which partly overlap with the symptoms of depression. Behavioral activation may help break the vicious circle by helping schizophrenic patients restore positive experiences by means of training to monitor daily activities, evaluate values and goals, and establish a program of activities to fulfill these goals. The aim of this form of therapy is to increase the level of activities

(routine, social activities) that are pleasurable, valuable and inspiring for the patient. However, the pilot studies have failed to demonstrate clear conclusions in terms of the efficacy of this technique with respect to negative symptoms of schizophrenia [68, 69].

Furthermore, the treatment of schizophrenia also involves metacognitive training (MCT) as a form of treatment supplemental to pharmacotherapy and other therapeutic interventions. The studies evaluating the effect of MCT on negative symptoms revealed a reduction in their severity relative to baseline values, but no statistical superiority of MCT was found when compared with control groups (cognitive remediation or standard social skills training). Other studies showed that metacognitive training brings clinical benefits in the treatment of schizophrenia in terms of improving, for example, metacognitive skills, social functioning, patient quality of life, and general severity of illness symptoms. However, no significant effects of this intervention were noted with respect to negative symptoms of schizophrenia [70, 71].

Other interventions

Next to pharmacotherapy, other biological interventions are also used in the treatment of schizophrenia. With respect to negative symptoms of schizophrenia, transcranial magnetic stimulation (TMS) receives the most research attention in this group of interventions. It is a painless and non-invasive method to stimulate the central nervous system; in the mechanism of electromagnetic induction, it elicits current flow in the stimulated regions of the cerebral cortex, leading to their activation. Stimulation with multiple series of stimuli (repetitive TMS, rTMS) and repeating stimulation sessions (even up to 8 session a day for 5 consecutive days in intensive protocols or one session daily for 3–6 weeks in protocols involving longer time periods) activate pyramidal neurons, thereby reinforcing existing synaptic connections and facilitating the creation of new ones [72]. This treatment mechanism is particularly relevant in, amongst others, deficit schizophrenia. The efficacy of rTMS in the treatment of negative symptoms of schizophrenia has been evaluated in a dozen or so sham-controlled, randomized clinical trials, and their results have been mostly positive [73]. This has become the rationale to design and perform a large multicentre study [74]. Unfortunately, it ended with a negative outcome. The efficacy of rTMS in the treatment of schizophrenia with negative symptoms was not confirmed, and the objective of obtaining FDA authorization of left dorsolateral prefrontal rTMS in the treatment of schizophrenia with deficit symptoms drifted far away. At present, the class of recommendation and level of evidence for this method in negative symptom management are assessed as IIb/B, which means that this method “may be considered.”

Other interventions evaluated in the treatment of schizophrenia with negative symptoms encompassed light therapy and EEG biofeedback trainings. The available data, however, do not permit one to acknowledge these methods as potentially effective in the treatment of negative symptoms. Other important research directions include

attempts to treat schizophrenia using novel technologies: virtual reality (VR), mobile applications and wearables. The first published randomized clinical trials indicate that of these three methods VR carries the greatest potential to become broadly used in the treatment of schizophrenia [75] but perhaps more in cognitive rehabilitation or social skills and interaction training than in the treatment of negative symptoms.

Recapitulation

The following conclusions have been drawn:

1. Psychoeducation is a key. Each person suffering from a severe mental illness has the right – beside the legal right to be informed by professionals – to receive situation-adequate information about their illness, its causes, course and different treatment options. Patient awareness is the fundament of cooperation when making clinical decisions and is essential to undertake health-oriented behaviors. In order to optimize gathering knowledge about the illness and to lower the risk of illness recurrence, a structured psychoeducation program should be offered for a sufficient amount of time and – if needed – on multiple occasions as part of the global treatment plan. The patient's family should be included. However, psychoeducation is not a high-efficacy intervention in the treatment of negative symptoms of schizophrenia (level of evidence: B, class of recommendation IIb).
2. Family group psychotherapy enriches the patient and their family by providing them with experiences of similar families; it has a socializing value, which is stimulating, while negative symptoms are more pronounced in a non-stimulating environment. Family attitudes are improved, criticism is reduced, clear communication appears with realistic judgement concerning possibilities and limitations. Patients may benefit especially from cognitive behavioral psychotherapy, in the form of both individual therapy and group therapy (level of evidence B, class of recommendation IIa).
3. Emotional intelligence (EI) training does not affect the ability of emotional processing and expression, but it does improve cognitive elements of social cognition and empathy. It does not have a statistically significant impact on negative symptoms (level of evidence B, class of recommendation IIb). Social skills training (SST) is important in social rehabilitation and improves social functioning, especially in outpatients. It should be implemented in the comprehensive therapy in accordance with individual patient needs. Single studies indicate the efficacy of SST in improving negative symptoms, interpersonal communication and quality of life (level of evidence B, class of recommendation IIa). Mindfulness training is effective in improving illness insight, lowering symptom severity and minimizing relapses (level of evidence B, class of recommendation IIb).
4. As severe mental illnesses are often associated with the impairment of activities of daily living and social functions, which makes it very difficult to participate in

social life, psychiatric rehabilitation is highly important as it helps to shape one's own life and enables participation in social activity in various aspects of living (self-care, family, leisure, work, participation in social life). Psychiatric rehabilitation should be offered to patients with severe mental illnesses as a part of the global treatment plan and based on individual patient needs and preferences (level of evidence A, class of recommendation IIa).

5. Cognitive remediation or cognitive trainings are effective and patient-accepted methods to treat cognitive deficits in schizophrenia or schizoaffective disorder; they offer improvement, restoration or compensation for impaired cognitive functions, thus improving patient daily functioning. This relieves negative symptoms of schizophrenia (level of evidence B, class of recommendation IIa).
6. Physical activity is a valuable form of therapy in schizophrenia. Being supplemental to pharmacotherapy, it may lead to the reduction of the severity of negative symptoms and facilitate the improvement of patient functioning and their quality of life (level of evidence B, class of recommendation IIb).
7. Continuing and undertaking regular physical activity on a daily basis should be encouraged and recommended. Depending on symptoms and tendencies as well as physical abilities, physical interventions are used as a part of the global multimodal therapy.
8. Next to pharmacotherapy, other biological interventions are also used in the treatment of schizophrenia. The efficacy of rTMS and therapies utilizing virtual reality or mobile applications is still being investigated. The available data, however, do not permit one to acknowledge these methods as potentially effective in the treatment of negative symptoms of schizophrenia (level of evidence and class or recommendation for rTMS: B/IIb, and for the remaining methods: C/IIb).

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