# Factors influencing the outcome of integrated therapy approach in schizophrenia: A narrative review of the literature

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The integration of pharmacotherapy with psychosocial interventions has an important role to play in the improvement of functional outcome of subjects with schizophrenia (SCZ), in all stages of the disorder. It is essential for the adequate management of unmet therapeutic needs, such as negative symptoms and cognitive dysfunctions which account for most of the functional impairment of subjects with SCZ and do not respond to available antipsychotics. Enhancing the knowledge on factors involved in the effectiveness of integrated treatment plans is an important step forward for SCZ care. This review aims to identify factors that might influence the impact of integrated treatments on functional outcome. Most studies on the impact of psychosocial treatments on functional outcome of subjects with SCZ did not control for the effect of prescribed antipsychotics or concomitant medications. However, several factors relevant to ongoing pharmacological treatment might influence the outcome of integrated therapy, with an impact on the adherence to treatment (e.g., therapeutic alliance and polypharmacotherapy) or on illness-related factors addressed by the psychosocial interventions (e.g., cognitive dysfunctions or motivational deficits). Indirect evidence suggests that treatment integration should consider the possible detrimental effects of different antipsychotics or concomitant medications on cognitive functions, as well as on secondary negative symptoms. Cognitive dysfunctions can interfere with participation to an integrated treatment plan and can be worsened by extrapyramidal or metabolic side effects of antipsychotics, or concomitant treatment with anticholinergics or benzodiazepines. Secondary negative symptoms, due to positive symptoms, sedation, extrapyramidal side effects or untreated depression, might cause early drop-out and poor adherence to treatment. Researchers and clinicians should examine all the above-mentioned factors and implement appropriate and personalized integrated treatments to improve the outcome of SCZ.

KEYWORDS

antipsychotics, psychosocial interventions, side effects, treatment adherence, cognitive impairment, negative symptoms

## Introduction

Schizophrenia (SCZ) is a complex and severe mental disorder. Evidence suggest that its clinical phenotype is the result of the interaction among genetic, biological, psychological, social and environmental factors. As a matter of fact, SCZ clinical phenotypes are very heterogeneous in terms of psychopathological features, risk factors, comorbidities, response to treatment and personal developmental trajectories (1–11).

The disorder is ranked among the 15 leading causes of disability worldwide (12): subjects with schizophrenia show a shorter lifespan than the average general population, are at increased risk of suicide, and of physical health problems (e.g., cardiovascular and lung illnesses, cancers, and obesity) and have a poor quality of life and functional outcome (2, 13–19), with only 15% of patients reaching criteria for clinical recovery (20–22).

The impairment in functional outcome includes deficits in self-care, interpersonal relationships, everyday life skills and work abilities, even during periods of remission from active psychosis (5, 13, 14, 16, 23–27). Several variables, some related to the illness, others to personal resources, and others to the context in which the person lives, seem to influence the functional outcome of subjects with schizophrenia, through direct or indirect relationships (5, 13, 14, 16, 26–28). Among the illness-related variables, negative symptoms, deficits in cognitive functions (neurocognition and social cognition) and functional capacity account for most of the functional impairment of patients and still represent unmet therapeutic needs (5, 16, 25–27, 29). These aspects are present since the onset and the early stages of the disorder, often predate it and show an elevated stability along the course of the illness (30–35).

The personal resources refer to resilience, coping strategies, healing styles and self-esteem; context-related variables include socio-economic status of the family, financial and employment opportunities, family and social incentives, stigma and social network (5, 13, 14, 16, 25–27, 36).

The relationships among these variables and functional outcome seem to be very complex and to follow multiple and complicated pathways (5, 16, 26, 27, 37). For instance, it has been found that neurocognition influences the functional outcome, in particular the areas of everyday and work skills, mainly indirectly through functional capacity, social cognition, engagement with services, and internalized stigma, which in turn is indirectly associated with the functional outcome through the resilience (16, 27). Negative symptoms belonging to the Experiential domain (avolition, anhedonia, and asociality), influence the functional outcome, in particular the area of interpersonal relationships, both directly and indirectly, through internalized stigma, resilience and engagement with services (16, 27).

Furthermore, it has been found, by using network analyses, that functional capacity and everyday life skills emerge as the most central and interconnected nodes (5, 26, 37). Functional capacity is the bridge between cognition (neurocognition and social cognition) and functional outcome (5, 26, 37), in particular the area of everyday life skills which, in its turn, connects other domains of functional outcome with psychopathology and internalized stigma (5, 26). The two domains of negative symptoms (the Experiential domain and the Expressive one) have different associations with functional outcome: the former one, defined above, with interpersonal relationships and work skills, while the latter domain, consisting of blunted affect and alogia, is connected with everyday life skills (5, 26, 37).

Understanding the complex relationships among multiple factors and functional outcome may foster the implementation of recovery-oriented and integrated treatment programs (psychosocial and pharmacological), that might be individualized according to patient's needs, to reduce symptom severity and improve patient's functional outcome, thus increasing the possibility of recovery (38–41). To date, the use of antipsychotics represents the main treatment strategy to provide patients with an effective symptom control and clinical stability (38–42). However, pharmacological treatments are most effective at reducing positive symptoms, but do not target adequately some aspects of schizophrenia, such as negative symptoms, cognitive impairment, and functional outcome. In addition, medication adherence is often poor (42–44), leading to high rates of relapse and hospitalization. Therefore, psychosocial interventions are usually provided in addition to pharmacotherapy and play an important role in the treatment of schizophrenia, in particular in improving functional outcome.

Different modalities and combinations of psychosocial interventions have been developed with the aim to address the complex individualized needs of patients (38, 40, 45), including the management of negative symptoms and cognitive dysfunctions (38–41, 46–48), to improve patient's reintegration in the community, promote recovery, and support patients and their families (38, 40, 41, 49, 50). Some psychosocial interventions, such as psychoeducation and cognitive behavioral therapy (CBT), allow patients to gain knowledge about their illness; others, such as cognitive remediation, social skills training, and supported employment may enhance adaptive skills (45). These interventions are briefly described below.

## Psychoeducation

Psychoeducation is an intervention that aims to provide patients and their families with information about the disease and its treatment, as well as disease management problem-solving and coping skills and to access community mental health-care services. It allows to establish a collaborative

relationship between mental health providers, patients and their caregivers, helping them to reduce the burden of the disease and develop recovery strategies (40). This intervention is effective in reducing relapses, hospitalization, stigma and increasing patient's adherence to treatment and has an impact on various functional determinants, such as resilience, stigma, active participation in shared decision-making, ability to ask for service help when necessary, thus improving their quality of life and the overall functioning (38, 40, 45).

## Cognitive behavioral therapy

CBT aims to modify dysfunctional beliefs, by helping subjects to understand the link between perceptions, beliefs, emotional and behavioral reactions. This intervention has proven effective in reducing the intensity of or distress related to positive symptoms and improving overall functioning (6, 38, 40, 45), including work and social functioning (51–54).

## Cognitive remediation

Cognitive remediation for schizophrenia is a behavioral training-based intervention aimed to determine an improvement of individual's cognitive functions (51, 52). Several different interventions have been developed; they can have an individual or group format, use pen and paper or computerized modalities, including bottom-up or top-down strategies or include different combinations of these elements and can also vary in the frequency of sessions and the duration of treatment programs (55). Cognitive remediation usually utilizes exercises aimed at improving cognitive deficits in clinically stable patients with schizophrenia and has found to have a consistent small-to-moderate positive effect on cognitive functions (mainly attention, executive functions, social cognition, and metacognition) (38, 40, 45, 56–60). It has a positive effect also on work and social functioning (60), probably mediated by improvement in cognitive domains (58, 59, 61), particularly when it is combined with other rehabilitation techniques, such as psychoeducation and training to develop social, vocational and daily living skills (45). In addition, this intervention has demonstrated efficacy in improving negative symptoms (29, 60, 62–65).

## Social skills training

Social Skills Training is a psychosocial therapy that is based on the discussion of the contextual (setting), non-verbal (body language), and paralinguistic (voice tone) aspects of interpersonal interactions (66, 67). It is an intervention of proven effectiveness to improve social skills in subjects with schizophrenia (38, 40, 45). It has an impact also on cognitive deficits, negative symptoms and psychosocial functioning (29, 64, 66, 68, 69) and has proved effective when associated with cognitive remediation or supported employment (45).

## Supported employment interventions

Furthermore, taking into account that subjects with schizophrenia are 6–7 times more likely to be unemployed than those without such disorders, supported employment interventions, especially when integrated with cognitive remediation and social skills training, might be implemented to help patients to obtain competitive employment, work longer and have higher salaries than persons without such support (38, 40).

## Early intervention

A meta-analysis of 10 randomized clinical trials was conducted in the early phases of schizophrenia with the aim to compare integrated treatment (different modalities of psychosocial interventions in conjunction with antipsychotics) with "pharmacological treatment as usual". This study has demonstrated that early integrated treatment was better than "treatment as usual" in favoring control of symptoms, reduction of relapses and hospitalization rates, adherence to treatment, involvement of the subject in school or work activities, and improvement of the quality of life and global functioning (70). Therefore, early integration of psychosocial interventions with pharmacological treatments should be encouraged (71).

## Factors influencing the outcome of integrated treatment in schizophrenia

However, despite the recognition of the advantages of early, individualized and integrated treatment plans to improve patient outcomes, some difficulties might be encountered in the implementation of evidence-based integrated treatment protocols in clinical settings. For instance, predictors of treatment response are still unavailable. Failure to achieve progress in this direction might be due to the lack of control for potential confounding factors: in fact, in most studies, antipsychotics or concomitant medications prescribed to patients participating in a clinical trial have been typically designated as "standard treatment" or "treatment as usual", and not systematically evaluated (39, 72). However, several factors relevant to the ongoing pharmacological treatment might influence the outcome of integrated therapy, with an impact on the adherence to treatment (e.g., therapeutic alliance and polypharmacotherapy) or on illness-related factors

**FIGURE 1**
Factors influencing the impact of integrated treatment on functional outcome.
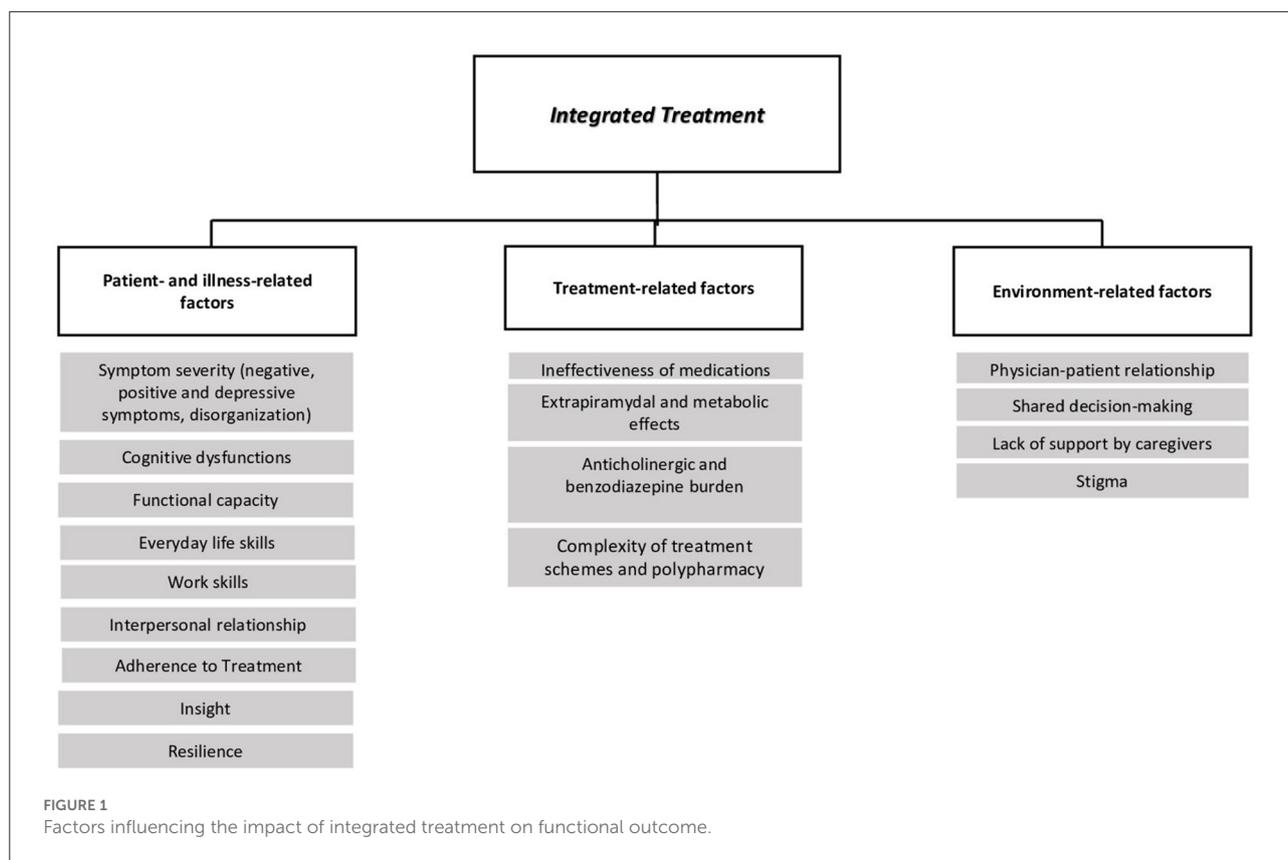
addressed by the psychosocial interventions (e.g., cognitive dysfunctions or negative symptoms). The integration of treatments should consider the possible detrimental effects of different antipsychotics or concomitant medications on cognitive functions, as well as on secondary negative symptoms (38, 39, 42, 73). Cognitive dysfunctions can be worsened by extrapyramidal (74, 75) or metabolic side effects of antipsychotics (76), or concomitant treatment with anticholinergics or benzodiazepines (77–79). Extrapyramidal side effects, sedation, positive symptoms, or untreated depression might cause secondary negative symptoms and lead to poor adherence to treatment (38, 42, 80).

In this manuscript we will provide clinicians with an overview of factors that might influence the impact of integrated pharmacological and psychosocial treatments on functional outcome (Figure 1). We will highlight areas of interaction between treatments with potential confounding factors, including medication side effects, patient adherence to treatment, cognitive dysfunctions and negative symptoms.

## Methodology

For this review, we searched PubMed for articles in English published until January 2022, including the following terms: [(psychosis OR schizophrenia OR "Psychotic disorders") AND (SGA OR "second generation antipsychotics" OR FGA OR

"first generation antipsychotics" OR psychopharmacology OR antipsychotics) AND ("psychosocial rehabilitation" OR "psychosocial interventions")] OR [(psychosis OR schizophrenia OR "Psychotic disorders") AND "integrated treatment"]. We focused on five reviews and one meta-analysis. In addition, additional hand-searching was performed to identify publications relevant to the topic that were missed by the search strategy. Therefore, 32 reviews and 29 meta-analyses were included by hand search. Original landmark studies were selected from the reference list of reviews and meta-analyses.

## Pharmacotherapy

Antipsychotic treatment provides substantial benefits on symptom dimensions in schizophrenia spectrum disorders and represents the cornerstone of clinical stabilization, a condition in which psychotic symptoms are absent or of mild/moderate severity and require no treatment changes and/or hospital admissions. This condition is necessary to implement an effective integrated treatment plan (81). In fact, stable antipsychotic treatment is required to avoid symptom exacerbations and relapses (82), and implement non-pharmacological interventions, thus improving patients' outcomes (83–85). Antipsychotic treatment relies mostly on first generation (FGA) and second generation (SGA) antipsychotics. FGA are potent antagonists of dopamine D2 receptors

(responsible for the antipsychotic effect), as well as adrenergic, cholinergic and histaminergic receptors (responsible for the high rates of side effects) (86). On the other hand, SGAs have a lower affinity for the aforementioned receptors, and they block the 5HT2A receptor (13), thus having reduced extrapyramidal side effects (86), but with comparable rates of adverse events such as sedation and weight gain, with respect to FGA (13).

Along with antipsychotic drugs, many individuals with schizophrenia require other types of medications, such as anticholinergics, benzodiazepines, antidepressants and mood stabilizers.

In most clinical trials evaluating the effectiveness of an integrated therapy, type and dosage of prescribed antipsychotics or concomitant medications have typically been designated as "standard treatment" or "treatment as usual" and not systematically evaluated (39, 72). However, some factors relevant to ongoing pharmacological treatment, such as the appearance of side effects, might impact different aspects, for instance adherence to treatment, cognitive functions, negative symptoms, and influence outcome. Within an integrated treatment plan, clinicians should carefully take into account the type and dosage of ongoing pharmacological treatments, in order to rule out the possible detrimental effects of pharmacotherapy on the outcome of the interventions.

## Pharmacological treatment side effects

Antipsychotics are associated with several side effects, sometimes severe ones, which can reduce adherence to treatment, thus leading to a reduction or loss of clinical stability, which in turn may affect the outcome of an integrated therapy (38, 87–90). The influence of side effects on treatment adherence, cognitive abilities and negative symptoms will be described more in depth in the paragraphs 4–6.

Common side effects are represented by motor symptoms and cardiometabolic effects. In general, first-generation antipsychotics (FGAs) are associated with motor side effects, while second-generation antipsychotics (SGAs) with weight gain and metabolic issues (75, 91–95).

Motor symptoms, commonly referred to as extrapyramidal symptoms (EPS), affect movement and muscle tone and can lead to parkinsonism (tremor, muscle stiffness and bradykinesia), muscle spasms (dystonia), subjective and objective restlessness (akathisia), involuntary and repetitive movements of the trunk, limbs, tongue and jaw, i.e., dyskinesia (96, 97). Literature widely reports a higher prevalence of EPS in subjects treated with FGAs, as compared to subjects treated with SGAs (75, 98–101). The higher incidence of EPS during treatment with FGAs, as compared to SGAs, could lead to poor treatment adherence and therefore compromise the clinical stability of the subject (75). In addition, EPS might worsen cognitive deficits and cause secondary negative symptoms in schizophrenia, thus

indirectly influencing the outcome of an integrated treatment (29, 75, 102, 103).

The cardiometabolic effects include weight gain and metabolic syndrome, which refers to the presence of at least three out of the five following criteria: increased waist circumference, hypertriglyceridemia, reduced high-density lipoprotein (HDL), elevated blood pressure, and elevated fasting glucose (76, 92). It has been shown that metabolic effects can adversely affect cognitive performance in subjects without psychiatric disorders and also in subjects with schizophrenia (104–111), thereby worsening the outcome of an integrated treatment.

Other side effects to be ascribed to a different extent to all antipsychotics are represented by changes in cardiac electrical activity, hyperprolactinemia, anticholinergic adverse effects, sedation, decrease of the seizure threshold, sialorrhea, neutropenia and agranulocytosis, and neuroleptic malignant syndrome (112–115).

Besides being poorly tolerated by the patient, the presence of side effects seriously affects patient's general health, is associated with less favorable attitudes toward antipsychotic treatments and, consequently, leads to a reduction in adherence to treatment, thus compromising the efficacy of an integrated treatment (38, 76, 89, 116).

Besides the impact of antipsychotic drugs, other treatments can influence the outcome of an integrated treatment in subjects with schizophrenia. In particular, long-term co-treatment with benzodiazepines has been seen to impair cognitive abilities, both through a direct or indirect mechanism (mediated by the effects of their potential sedation) (76, 117–120).

Furthermore, long-term co-treatment with anticholinergics drugs, often used to reduce extrapyramidal symptoms, is associated with poor adherence to drug treatment (121) and with a worsening of pre-existing cognitive dysfunctions (78, 79, 117, 122–128), while the progressive dosage reduction of anticholinergics is accompanied by a positive effect on cognition (129).

In the light of the available evidence, when evaluating the outcome of a psychosocial intervention targeting for instance cognitive dysfunctions, it is important for clinicians to rule out the potential confounding effects of anticholinergic or benzodiazepine drug treatments on cognition. The influence of concomitant medication side effects on cognitive abilities will be described more in depth in paragraph 5.

## Adherence to treatment

Available evidence suggests that the access of patient to additional treatments other than pharmacotherapy is influenced by the clinical stability, defined as the absence of relapses, which require the hospitalization or substantial changes of ongoing pharmacological treatments (42, 130). By preventing relapses, the use of antipsychotics represents the main strategy to ensure clinical stability (38, 47). However, a poor treatment adherence

still represents a major issue in the care of subjects with schizophrenia (38, 47, 59, 60), affecting about 50% of the patients (42–44). The lack of treatment adherence increases relapse and hospitalization rates (131); however, it is has been noted that it is difficult to state whether non-adherence is the cause of relapses and hospitalizations or whether it represents an indicator of disease progression (38, 132, 133).

The adherence to antipsychotics is influenced by several factors, some related to the patient (e.g., poor insight, neurocognitive dysfunctions, symptoms severity or lack of symptom improvement), some to medication (e.g., ineffectiveness of or adverse effects of medications, complexity of treatment schemes, and polypharmacotherapy) and some to patient's environment (e.g., lack of support by caregivers, poor physician-patient relationship, non-shared decision making, and lack of information about the disease and its treatment) (42, 73, 134).

Poor insight is regarded as one of the main causes of treatment non-adherence in subject with schizophrenia (42, 43, 73, 135–138). Indeed, individuals with a better awareness of their pathology have better attitudes toward drugs, thus leading to better adherence and therapeutic results (135). Conversely, individuals who are unaware of their condition will be less motivated to resolve their symptoms and will not need their symptoms to be managed, thus leading to poor therapeutic results and great likelihood of relapses (73, 135, 139). Poor insight and non-adherence to treatment appear to contribute directly to a worse response to integrated therapy, leading to a poor outcome (140).

Neurocognitive impairment can adversely affect adherence to treatment, as it impairs processes that are fundamental for adherence, such as attention and memory, leading to a difficulty in understanding or managing the programs of therapy, especially when the treatment schemes are very complex (141–144). However, some studies did not find a relationship between cognitive impairment and non-adherence to treatment (139, 145–152).

Lack of symptom improvement (due to the ineffectiveness of medications), with a worsening of positive and/or negative symptoms, might represent a potential factor for non-adherence to treatment (42, 80, 116, 153–155). However, some studies did not find an association between symptom severity and adherence rates (156, 157).

Furthermore, it has been reported that adverse effects of antipsychotics have an important role in the adherence to treatment. Indeed, they can lead to the discontinuation of therapy (38, 158, 159), due to patients' poor tolerability toward these effects (160).

In the general population, and particularly in individuals over the age of 65, polypharmacy is more frequently associated with non-adherence to treatment simply because of the large number of medications that subjects can forget to take daily (160–162). Also for subjects with schizophrenia, polypharmacy

and the complexity of treatment schemes have been associated with non-adherence to therapy (38, 42, 43, 80, 163–170); in a recent study it was shown that the risk of non-adherence is about double in subjects who take more than one drug compared to those who take monotherapy (80, 171). However, it is also possible that polypharmacy indirectly affects adherence to treatment, due to an increase in the number of side effects (172, 173).

Adherence to treatment is favored by a good physician-patient relationship, through a better understanding of the individual motivation to treatment and by involving the patient in treatment plans and decisions (shared decision making). Indeed, the shared decision-making approach, taking into account patient's preferences, increases the motivation to treatment and, consequently, treatment adherence (174–183). In addition, it has been demonstrated that strong therapeutic relationships with a good therapeutic alliance are related to a decrease of symptom severity, hospitalizations, drop-out rates and to an increase in treatment adherence (48, 183, 184), while poor therapeutic relationships have been shown to increase the risk for non-adherence (40, 43, 185).

Within the integrated treatment approach, it is crucial to identify the possible causes that underlie non-adherence to treatment, exploring patient's individual needs, preferences, satisfaction, in order to establish an adequate treatment plan (40, 42, 186).

To improve adherence to treatment of subjects with schizophrenia spectrum disorders, it is preferable to (i) improve insight of patients with poor or no awareness of their disease, (ii) reduce negative attitudes toward drugs, (iii) improve cognitive functions, (iv) reduce symptom severity, (v) avoid, when possible, the use of polypharmacotherapy or complexity of treatment schemes, and (vi) involve patients in the treatment decision-making process through a good therapeutic alliance.

## Cognitive dysfunctions

Cognitive dysfunctions, which are defined as deficits of different cognitive domains (speed of processing, attention and vigilance, working memory, verbal learning and memory, visuospatial learning and memory, reasoning and problem solving, and social cognition) (187–191), represent a crucial domain to be targeted within an integrated treatment approach. They are present since the onset and the early stages of the disorder, often predate it and are associated to poor premorbid functioning, and show an elevated stability along the course of the illness (30, 33). Cognitive dysfunctions account for most of the functional impairment of patients, are poorly responsive to antipsychotic treatments, thus still represent an unmet therapeutic need (5, 16, 26, 27, 192–194). Different reviews and metanalyses reported that cognitive remediation therapy, skills-based training and physical exercise,

represent good treatment strategies that might be used as part of an integrated treatment to improve cognitive impairment of subjects with schizophrenia (56–60, 69, 195–199). Other psychosocial interventions, such as cognitive behavioral therapy and psychoeducation, which have been shown to improve psychosocial functioning, caregiver's burden and measures related to overall wellbeing (psychoeducation), could be effective in improving cognitive dysfunctions, but more research is needed to properly assess their effectiveness on this domain of functioning (51–54, 192, 200–203).

Despite the reports of psychosocial interventions efficacy in ameliorating cognitive deficits, the treatment response rate is very heterogeneous (204). Some potential predictors of treatment response, such as participants' age, premorbid IQ, duration of illness and of treatment have been investigated in previous studies (204). The duration of the psychosocial intervention might also have an effect on outcome, and the number of training sessions and the overall duration of the interventions show a great degree of variation between studies, depending on the type of intervention (47). For cognitive remediation, it is recommended that the intervention should be of sufficient intensity and duration to determine an enduring improvement of cognitive functions (205). Most psychosocial interventions typically extend up to 6 months with 1-h sessions, 2–5 times a week (47). However, no systematic investigation of the duration has been carried out and more studies are needed in order to find out whether longer training sessions and a greater number of sessions lead to a further improvement of cognitive functions and better functional outcome and whether the influence of intensity and duration of training sessions varies according to the type of intervention (204). In addition, further investigation of predictors of response to treatment and potential confounding factors influencing the outcome is needed (204).

According to available meta-analyses SGAs were consistently superior to FGAs in improving cognitive functions, with no molecule consistently outperforming the others (194, 206–209). A recent meta-analysis (210) reported favorable effects for amisulpride, quetiapine, lurasidone, olanzapine, perphenazine, risperidone, sertindole, and ziprasidone, while remoxipride, clozapine and haloperidol, were outperformed by placebo in most cognitive domains (210). The positive impact of perphenazine on cognition was discussed as an unexpected result by the authors of the meta-analysis, and in need of further replications (211). Overall, SGAs have been shown to be more efficacious in improving cognitive functions, as compared to FGAs; however it is questionable whether this advantage reflects a real improvement of cognitive functions or a lower burden (as compared to FGAs) of extrapyramidal side effects that might worsen cognitive functions (212).

Besides the type of antipsychotic, also the dose seems to influence cognition in subjects with schizophrenia (76): higher antipsychotic doses and polypharmacy are associated with worse cognitive functioning, and an improvement in different cognitive domains (memory, visuospatial, language, attention, and delayed memory) has been observed when the antipsychotic dose was reduced (76). Higher antipsychotic dosage has been found in association with lower cognitive functions after a cognitive remediation program, suggesting that patients with a more severe illness (who generally receive high doses of antipsychotics) had less benefit from cognitive remediation, or that, high antipsychotic doses limit the effectiveness of the intervention, due to the presence of EPS (213, 214). In fact, clinical practice and data collected from the literature show that EPS might worsen neurocognitive (74, 75, 215–221) and social cognition functions (75), thus influencing the outcome of a psychosocial intervention targeting them (74, 75, 215–221). Indeed, subjects with EPS had worse overall cognitive performance, with lower scores for attention, motor skills and verbal learning domains (74, 215–217, 219). Studies that focused only on tardive dyskinesia reported inconsistent results, since two studies found a relationship between tardive dyskinesia and deficits in spatial working memory, visuospatial skills, and attention (220, 221), while another study did not find any significant association between tardive dyskinesia and cognitive impairment (222).

To date, it is not clear which is the mechanism that underlies the relationship between EPS and neurocognitive deficits; however, some theories have been developed: subjects that develop EPS, as compared to subjects that do not develop EPS, may have pre-existing neural dysfunctions, which could explain both greater vulnerability to develop EPS and worse cognitive performance after treatment with antipsychotics (223), or EPS might affect those motor skills required to perform specific neurocognitive tasks. Indeed, Fervaha et al. demonstrated that subjects with schizophrenia and EPS had a lower cognitive composite score than subjects without EPS, but this result was not confirmed after controlling for the effect of motor speed (74). However, this hypothesis explains the association between EPS and performance of only those cognitive tasks involving timed tests or motor movements, but not the others (e.g., verbal learning and social cognition) (75).

The metabolic syndrome is present in about 33.5% of subjects with schizophrenia. Different risk factors are associated with the appearance of this syndrome: lifestyle factors, such as smoking, poor eating habits and sedentary behavior, antipsychotic medications, as well as genetic factors relevant to schizophrenia and/or to treatment response that overlap with genes related to metabolic functions (224). Most studies reported an association between metabolic effects and cognitive dysfunctions, both in subjects without psychiatric disorders (104–108) and in those with schizophrenia (76, 109–111). In particular, in subjects with schizophrenia, the metabolic syndrome seems to influence negatively some cognitive functions, such as processing speed, memory, attention, and reasoning and problem solving (109–111).

Conversely, other studies failed to find this association (225–227). However, some of these studies, with the exception of the CATIE trial, have found that specific aspects of metabolic syndrome, such as hypertension, were correlated with lower cognitive scores, whereas other factors, such as increased waist circumference and dyslipidemia were less consistently associated with general impairments of cognition in schizophrenia (226, 227). Furthermore, in one study, hyperglycemia was associated with better verbal memory performance (226). Further studies examining the associations between individual metabolic symptoms and cognition in subjects with schizophrenia are needed to draw sound conclusions (76).

The anticholinergic burden has been related to the risk of cognitive impairment both in elderly subjects and in subjects with schizophrenia (78, 79, 228–230). Several large and well-conducted studies have shown an association between the use of drugs with anticholinergic properties (some antipsychotics and anticholinergic drugs) and poor cognitive performance, with the anticholinergic burden increasing cognitive impairment in specific domains (e.g., processing speed, attention, language, problem solving, and psychomotor performance) (78, 123–125, 127, 231–235). Another study showed that exposure to drugs with anticholinergic properties impairs attention and declarative memory in schizophrenia, but has no effect on other aspects of cognition, including intelligence, working memory, executive functioning, and motor speed (236). One study detected the possible impact of the anticholinergic burden on the outcome of a cognitive remediation program, and found that the serum level of anticholinergic activity, measured by radioreceptor assay, at baseline negatively predicted cognitive remediation-induced changes, indicating that this variable had a negative impact on the patient's response to the intervention (235).

Patients with schizophrenia are often prescribed benzodiazepines as adjuvant drugs. Long-term use of these drugs has been shown to negatively impact cognition, and adverse effects have been reported on specific cognitive abilities, such as attention and working memory (77, 120). Benzodiazepines represent a specific factor contributing to worsening of cognitive functions not only in individuals with schizophrenia, but also in the elderly (237) and progressive reduction in benzodiazepine dosage has been associated with improved cognitive functions (118, 119).

As part of an integrated treatment aimed at improving cognitive functions, clinicians should take into account some factors that could influence cognitive abilities, such as the type and dosage of used drugs, adherence to treatment and pharmacotherapy side effects. To avoid a negative impact on cognitive functions, clinicians should favor the use of molecules that have a low impact on these functions and limit the burden of anticholinergics and benzodiazepines, particularly in long-term treatment (77–79).

# Negative symptoms

Negative symptoms are a complex and heterogeneous construct with a pivotal role in the care of subjects with schizophrenia. They are present since the onset and the early stages of the disorder, often predate it, are associated to poor premorbid functioning and functional outcome, and show an elevated stability along the course of the illness (31, 32, 238).

Negative symptoms include avolition, anhedonia and asociality, which cluster into the Experiential domain, and blunted affect and alogia, which cluster into the Expressive Deficit domain (102, 103, 203, 239–241). Different pathophysiological features and different associations with patient's functioning have been found for the two negative symptom domains, thus implicating potential different treatment strategies for them (5, 16, 26, 27, 102, 103, 242–247). To date, there are no pharmacological treatments of proven efficacy for negative symptoms, particularly for primary and persistent ones, which still remain an unmet need in the care of subjects with schizophrenia (29, 103, 248–251).

Different reviews and metanalyses reported that some psychosocial interventions, such as cognitive training and skills-based training, represent a good treatment strategy that might be used as part of an integrated treatment to improve negative symptoms (29, 60, 62–66, 68). The potential role of cognitive behavioral therapy in improving negative symptoms is not yet clarified, since most meta-analyses have found small or insignificant effects of CBT on negative symptoms (29). Overall, different sources of heterogeneity in studies focusing on psychosocial interventions should be considered. Indeed, most studies included in the above-cited metanalyses did not have negative symptoms as a primary outcome, and few studies defined a minimum threshold for negative symptoms at inclusion. Patient populations were small and very heterogeneous in terms of illness and treatment duration, as well as of psychopathological features. In addition, most studies in the meta-analyses compared the psychosocial intervention to "treatment as usual", without providing information on type and dosage of antipsychotics. Finally, most studies used a global/total score for the evaluation of negative symptoms and did not report specific information on the characteristics of these symptoms, most importantly they did not distinguish between primary and secondary negative symptoms.

Indirect evidence suggests that different confounding factors might influence the outcome of integrated treatments targeting negative symptoms, in particular the type of antipsychotic, as well as factors that might cause secondary negative symptoms (parkinsonism, positive symptoms, or depression). Therefore, before starting an integrated treatment plan, also aimed at improving negative symptoms, clinicians should be encouraged to carefully rule out the effects of these confounding factors.

As to antipsychotic drugs, it has been demonstrated that different types of antipsychotics have a different impact

on negative symptoms in subjects with schizophrenia (13, 29, 252). Amisulpride and cariprazine showed promising results in targeting predominant negative symptoms (253–255). Furthermore, a meta-analysis conducted by Fusar-Poli et al. (252) found a small improvement in negative symptoms with SGAs, but not with FGAs. Within the SGA, amisulpiride, clozapine, olanzapine, quetiapine, and risperidone have been shown to be more effective than FGAs in ameliorating negative symptoms (13). However, in these metanalyses, included clinical data were very heterogenous, and no specific information on the characteristics of negative symptoms, for instance on the differentiation between primary and secondary negative ones, was provided (29). Distinguishing between primary and secondary negative symptoms is an important clinical issue from a therapeutic and a prognostic point of view. Indeed, while primary negative symptoms tend to be persistent and treatment resistant (256, 257), secondary negative symptoms might be effectively treated, targeting the underlying factors (e.g., parkinsonism, positive symptoms, or depression) (102, 103). These factors represent possible confounders when evaluating the outcome of an integrated treatment plan targeting negative symptoms.

Antipsychotic drugs, for instance, and in particular FGAs as reported in the paragraph 3, may induce extrapyramidal side effects. Some of these side effects, in particular bradykinesia and hypomimia, might mimic expressive negative symptoms. Furthermore, excessive sedation can lead to decreased activity and/or amotivation. In these cases, the differential diagnosis is made through a longitudinal observation of the symptoms. An increase in the severity of negative symptoms following an increase in the dose of the drug suggests the presence of secondary negative symptoms. In addition, a standard clinical examination to evaluate the presence of other EPS, such as tremor or rigidity, may be useful to rule out or diagnose drug-induced parkinsonism. The presence of negative symptoms secondary to extrapyramidal effects or sedation due to antipsychotic treatment should be treated with a possible dose reduction or drug change, choosing antipsychotics with lower risk of EPS and sedation (29).

Negative symptoms may result from positive ones; for instance, patients' experiences of threat and fear due to persecutory thoughts or hallucinations can lead to social withdrawal. To assess the secondary nature of negative symptoms, clinicians should observe whether negative symptoms occur during periods of psychotic exacerbation or as a result of changes in pharmacotherapy, or whether these symptoms improve as hallucinations and delusions are ameliorated by the antipsychotic treatment. In the presence of negative symptoms secondary to positive symptoms it is appropriate to re-evaluate the antipsychotic treatment with respect to the dosage or type of antipsychotic (29, 258–260).

Due to the overlap between depression and negative symptoms, it is often difficult to distinguish between primary negative symptoms, secondary negative symptoms due to depression, and depression without negative symptoms (261, 262). Furthermore, the inability to express internal experiences and emotions in patients with schizophrenia can hinder the detection of depression (261). To assess the secondary nature of negative symptoms, clinicians should observe whether negative symptoms, e.g., the social withdrawal, might be induced by depression. In this case, the presence of sadness, hopelessness and/or guilt might suggest that the negative symptomatology is secondary to depression (263, 264). After detecting depressive symptoms, the use of an antipsychotic drug with antidepressant properties (e.g., quetiapine, amisulpride, cariprazine, aripiprazole, clozapine, and olanzapine), or the addition of an antidepressant drug and/or of cognitive-behavioral therapy should be considered (13, 29, 265–267).

In the clinical practice, the distinction between primary and secondary negative symptoms can be challenging and should be considered as part of the assessment. It may require a longitudinal observation which is not always feasible. Indeed, to evaluate the secondary nature of negative symptoms, clinicians should observe whether negative symptoms occur during periods of psychotic exacerbation or in concomitance with depressive symptoms or following changes in pharmacotherapy.

Therefore, as part of an integrated treatment aimed at improving negative symptoms, clinicians should rule out the effects of some confounding factors, such as the dose and the type of drug used, parkinsonism, positive symptoms, or depression (29, 102, 103, 261, 268–270). To allow a good management of negative symptoms, clinicians should optimize the psychopharmacologic treatment to control positive and depressive symptoms, as well as to limit the appearance of EPS, thus favoring the outcome of the integrated treatment (29).

## Discussion

Within the recovery-oriented approach in the care of subjects with schizophrenia, the need of integrated therapy, involving pharmacological treatment and psychosocial interventions, is widely recognized (38–41). Some important implications for the implementation of evidence-based practice for guiding integrated therapy in clinical settings emerged from the review of the literature reported in this paper.

First, antipsychotics represent the main treatment strategy to provide patients with an effective symptom control and clinical stability (38–42), which appears to represent a crucial condition to realize a structured and effective integrated treatment plan (81). In fact, stable antipsychotic treatment is required to avoid symptom exacerbations and relapses (82); clinical stability facilitates patient's engagement in non-pharmacological interventions, and increases the likelihood of a good outcome (83–85).

Second, psychosocial interventions are important to address the complex individual needs of patients, (38–41, 46–48), ameliorate negative symptoms and cognitive deficits, improve

patient reintegration into the community, favor the patient's employment and support patients and their families, thus promoting recovery (38, 40, 41, 49, 50). In addition, through a good therapeutic alliance, psychosocial interventions improve the patient's insight in the illness, favor the adherence to treatment plans, thus reducing the risk of drug discontinuation and relapses.

Third, effective psychosocial interventions, such as cognitive training and skills-based training, should be made available to subjects with cognitive impairment, poor social competence, and negative symptoms. Such interventions should be provided as early as possible given the fact that the above-reported impairments have been described since early stages of the illness and even before clinical onset (30–35). In addition, psychoeducation and CBT should be implemented in clinical practice since they improve treatment adherence and reduce relapses and the distress related to positive symptoms. The impact of these interventions on functional outcome seems to be improved by combining different treatment approaches, basing on patient's individual needs and issues and the stage of the disease: cognitive remediation combined with psychoeducation and training to develop social, vocational and daily living skills; or social skills training combined with cognitive remediation and supported employment (45).

Fourth, besides their positive effects on symptoms control, antipsychotics and concomitant medications may induce adverse effects, that might seriously affect patient's general health, favor negative attitudes toward treatment and, consequently, lead to a reduction in the treatment adherence, thus compromising the efficacy of an integrated treatment (38, 76–79, 89, 116). Given the presence of differences across the available drugs in terms of individual response and tolerability, the characterization of the individual patient with respect to psychopathological dimensions, physical health and comorbidities should guide the treatment choice (6, 271, 272).

Fifth, patient-focused perspectives in the treatment plans, individual preferences, and satisfaction, should be taken into account in order to promote treatment adherence, improve long-term outcomes and facilitate the implementation of personalized treatment for subjects with schizophrenia, by evaluating individual needs (175, 178).

Sixth, understanding the complex relationships among multiple factors and functional outcome may foster the development of new treatments and the personalization of integrated psychosocial and pharmacological treatment programs. Therefore, the assessment of different variables, some related to the illness, others to personal resources and others to the context, should be encouraged and implemented within the clinical practice, in order to understand the individual patient needs and to establish a recovery-oriented treatment plan.

Seventh, every effort should be made to conduct clinical trials with standardized and replicable methodology. In addition, it will be important that such studies are specifically designed to clarify the impact of multiple confounding factors on patient's outcome, as well as to clarify the points of interactions between different types of treatment (pharmacological and psychosocial treatments) on different schizophrenia domains, and in particular on those which still represent unmet therapeutic needs.

However, the above considerations should be read in the light of the limitations of the studies included in this review. Most information gathered with respect to the interactions between pharmacological and psychosocial treatment was inferred indirectly from articles in which this topic was not the main focus of the study.

In conclusion, further studies are needed to clarify the impact of different variables on the outcome of an integrated treatment plan. A better understanding of possible predictors of treatment response, or of factors that might influence the patient's outcome, could enhance the implementation of personalized and individualized recovery-oriented treatments in clinical settings (6, 273, 274).

## Author contributions

## Conflict of interest

## Publisher's note

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