Treatment-Resistant to Antipsychotics: A Resistance to Everything? Psychotherapy in Treatment-Resistant Schizophrenia and Nonaffective Psychosis: A 25-Year Systematic Review and Exploratory Meta-Analysis

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Background: Roughly 30% of schizophrenia patients fail to respond to at least two antipsychotic trials. Psychosis has been traditionally considered to be poorly sensitive to psychotherapy. Nevertheless, there is increasing evidence that psychological interventions could be considered in treatment-resistant psychosis (TRP). Despite the relevance of the issue and the emerging neurobiological underpinnings, no systematic reviews have been published. Here, we show a systematic review of psychotherapy interventions in TRP patients of the last 25 years.

Methods: The MEDLINE/PubMed, ISI WEB of Knowledge, and Scopus databases were inquired from January 1, 1993, to August 1, 2018, for reports documenting augmentation or substitution with psychotherapy for treatment-resistant schizophrenia (TRS) and TRP patients. Quantitative data fetched by Randomized Controlled Trials (RCTs) were pooled for explorative meta-analysis.

Results: Forty-two articles have been found. Cognitive behavioral therapy (CBT) was the most frequently recommended psychotherapy intervention for TRS (studies, n = 32, 76.2%), showing efficacy for general psychopathology and positive symptoms as documented by most of the studies, but with uncertain efficacy on negative symptoms. Other interventions showed similar results. The usefulness of group therapy was supported by the obtained evidence. Few studies focused on negative symptoms. Promising results were also reported for resistant early psychosis.

Limitations: Measurement and publication bias due to the intrinsic limitations of the appraised original studies.
Conclusions: CBT, psychosocial intervention, supportive counseling, psychodynamic psychotherapy, and other psychological interventions can be recommended for clinical practice. More studies are needed, especially for non-CBT interventions and for all psychotherapies on negative symptoms.

Keywords: treatment-resistant psychosis, dopamine supersensitivity, negative symptoms, psychotherapy, behavioral therapy, group psychotherapy, positive symptoms

INTRODUCTION

Schizophrenia affects approximately 1% of the population, usually starting in adolescence or young adulthood, frequently leading to persistent disability, with a high risk of suicide (8%). Despite the advance in antipsychotics treatment, approximately 30% of patients with schizophrenia show a poor response or no response to antipsychotics (1–7), demonstrating persistent positive symptoms (i.e., hallucinations, delusions). The experience of persistent delusions and hallucinations may result in further disability, poor prognosis, and risk of suicide (8, 9). Finally, treatment-resistant psychosis (TRP) is responsible for increasing health assistance expenditure. For instance, in the United States, treatment-resistant schizophrenia (TRS) adds more than 34 billion dollars in the annual direct medical costs (10).

In the presence of pharmacological treatment resistance, can nonpharmacological, psychotherapy-based interventions significantly overcome the therapeutic response deadlock? Which psychotherapy in combination with antipsychotics does work better? Finally, what are the limitations and the pitfalls of the research on psychotherapy in TRS and TRP?

This review aims to provide a critical, systematic overview covering the last 25 years of published results of all types of psychotherapy, as adjunctive or substitutive therapy, specifically in TRS or TRP patients, including early psychosis and psychotic onset. TRS and TRP for many patients are lifelong mental disorders with significant consequences on most functional domains (11, 12). TRS represents a severe condition with relevant clinical, social, and health costs and consequences (2). In clinical practice, the criteria to define TRS have not been always consistent over time (2). The first complete definition was introduced in the seminal article of Kane and collaborators (13) on clozapine efficacy in TRS. Most of the new proposed criteria require the lack of response to at least two consecutive treatments with antipsychotics; in most cases, one of the two antipsychotics should be an atypical one, of adequate dose and duration (≥7 weeks). An adequate dose of antipsychotic medication in the most recent report is defined as a daily dose of ≥400 mg chlorpromazine equivalence (14–17). The lack of response has been indicated as a relative change in the evaluation scales (i.e., ≥20% decrease in the Positive and Negative Syndrome Scale) (17). Psychotic symptom persistence has been demonstrated to cause distress and serious interference with functioning (18), complicating the clinical course of schizophrenia. Therefore, a large proportion of patients may never reach a functional recovery (19). These patients show poor global functioning and life quality (20, 21), increased drug abuse (6), and reduced cognitive performance compared to patients who respond to the treatment (22).

Persistent psychotic symptoms have been observed for 2 years after the initiation of symptoms in 15% of cases (23). In a 15-year follow-up study of patients affected by nonaffective psychosis, every psychotic episode has resulted in raising the probability to experience residual positive symptoms. At least 25% of patients showed persistent positive and negative symptoms after the first episode, while nearly 50% presented persistent symptoms after the fourth episode (24). According to this progression of symptoms persistence, the total number of treatment-resistant patients can increase up to 60% (25). Two forms of treatment resistance have been hypothesized: a type of resistance that is already present at the onset of the pathology, and a second one that develops later on during the trajectory of the disorder and after a period of successful response to antipsychotics (26–28). Remarkably, 82% of TRS had been reported to be resistant since their first episode of psychosis, while 18% of patients with TRS develop resistance after a period of adequate response. It has been reported that the first group could recognize a neurodevelopmental disorder with relatively normal dopaminergic function and prevalent aberrant cortical–subcortical dysfunction (29, 30). Clozapine, the prototypical second-generation antipsychotic, is considered the gold standard of pharmacological treatment for TRS (31–34), even if its superiority in comparison to other second-generation antipsychotics has been challenged in recent meta-analysis (16, 35, 36). Moreover, drug combinations strategies are often used in TRP (32, 37–39) and in the "ultraresistant patients," who do not respond or respond only partially to clozapine. It has been estimated that approximately 30% of patients who are treated with clozapine do not respond adequately (14, 40, 41). Clinical features at diagnosis can only partially predict resistance to the treatment: poorer premorbid functions, an earlier age at onset of positive symptoms, family history of schizophrenia spectrum disorder, longer duration of untreated psychosis (DUP) (26, 42–48), male gender, a history of specific substance abuse, severe negative symptoms, and presence of soft neurological signs (3, 23, 42, 47, 49–51). Functional and structural brain imaging has identified potential brain abnormalities related to treatment response or resistance, specifically at the level of the frontal cortex, basal ganglia, corpus callosum, and anterior cingulate. Nevertheless, correlations with brain abnormalities have still not been consistently replicated (52, 53). In our study, we included an exploratory meta-analysis to provide a quantitative synthesis of data from Randomized Controlled Trials (RCTs). The aim of this latter analysis was to compare the efficacy of an augmentation approach with cognitive behavioral therapy (CBT) versus treatment as usual (TAU) in patients with treatment-resistant schizophrenia.
Psychotherapy Approach toPsychosis
The so-called “Dodo Bird Verdict” has been suggested in many reports to indicate that different psychological therapies are of nonspecific or similar efficacy, but this view is controversial and can be contrasted by meta-analytic studies (54–59). Criteria to define evidence-based psychotherapy (EBP) have been established in youth psychiatry (60). The comparison between EBP and the usual care has shown a more effective performance in the former but advantages in the latter (61, 62). Some researchers have used befriending (BF), an atheoretical and manualized control therapy (63), as a nonspecific relationship that works as a control group, but it has been shown that this approach could have a therapeutic impact, too (64). Nevertheless, psychological interventions have become more widely accepted over the past two decades (65–67). The majority of recent publications consider CBT the elective psychotherapy for psychosis (68, 70) and other treatments are not frequently studied. In particular, the number of articles on the psychodynamic treatment of schizophrenia was very high from 1966 to 1987, with the decline starting after 1980; however, no one was centered on treatment-resistant schizophrenia (71). Mueser et al. observed that the published studies are “only a crude index of the current therapy in schizophrenia since a small fraction of psychodynamic psychotherapy practitioners publishes their treatment cases.” In the history of psychodynamic psychiatry and psychoanalysis, psychosis has been traditionally considered impervious to treatment. However, recent literature points out to the association between environmental factors, such as childhood adversity, and the development of psychotic experiences, psychotic symptoms, and diseases (72–79). In fact, trajectory-based approaches to study clinical consequences to potentially traumatic events (PTEs) have recently emerged. In particular, prototypical trajectories have been found across independent studies, and resilience seems to determine the modal response to adversity (80). Abnormal early-life experience, such as early relationships characterized by a “lack of affectivity” during the first year of life, has been suggested to be potentially pathogenic (81). This aspect should also be evaluated as psychologically determinant in contributing to the development of a psychotic disorder. Furthermore, recent literature has also shown the important role played by the therapeutic relationships in all psychiatric settings in predicting the outcome (82–84). It has also been evidenced how therapist attitude and characteristics in the relationship can influence the outcome specifically in TRS patients (85).

Therefore, in the last 20 years, there has been a growing interest in developing a psychological intervention for people who continue to experience psychotic symptoms despite adequate pharmacological treatment (14, 86–90). In early interventions on psychosis, psychotherapy is a potentially relevant part of the treatment, whereas the medication only might neither be sufficient nor efficient (44, 91–96). Medications can also determine a worse clinical condition and be detrimental, since they can have brain structural effects (97–99). Remarkably, antipsychotic treatment can result in further psychotic symptomatology at this stage, due to a dopaminergic supersensitivity effect, induced by the treatment itself (100–102).

It has been observed that early psychosis patients may present treatment resistance. In particular, approximately 20% continue to have significant residual positive symptoms after 12 weeks of comprehensive treatment (103). Nevertheless, in early psychosis, a psychological or an integrated therapy with an adequate dose of medication could be effective, maximize results, prevent relapses, achieve recovery, and overcome drug resistance. Studies on the prodromal phase of psychosis have demonstrated that psychological treatments can be effective in reducing transition to psychosis (103, 104). Also, studies on psychosis onset have shown that, in selected cases, psychological interventions can be more appropriated as the first choice than medications (86, 105–107). The National Institute for Clinical Excellence (NICE) (108) and the Schizophrenia Patient Outcome Report Team (PORT) guidance included cognitive behavioral therapy (CBT) in their preferred list of treatments for schizophrenia (108, 109).

MATERIALS AND METHODS
Aimed at achieving a high standard of reporting, we followed the procedures indicated by the 2009 update of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (http://www.prisma-statement.org/) (see Figure 1) (110).

Eligibility Criteria, Information Sources, and Search Strategy
We limited our search to those records related to TRP, TRS and psychotherapy of the last 25 years, from January 1, 1993, until August 1, 2018. Such timeframe owed to methodological considerations aimed at including studies relying on homogeneous diagnostic criteria. A systematic database search was performed on MEDLINE/PubMed, Web of Science/ISI Web of Knowledge, and Scopus. The following combinations of keywords have been used: “treatment resistant psychosis OR treatment resistance psychosis AND treatment-resistant schizophrenia OR treatment resistance schizophrenia AND psychotherapy,” “antipsychotic resistant response OR antipsychotic resistant response AND psychotherapy,” “clozapine resistance AND psychotherapy OR augmentation strategies,” “partial responders antipsychotics AND psychotherapy OR augmentation psychotherapy,” “clozapine non responders AND/OR poor responder antipsychotics AND psychotherapy OR augmentation psychotherapy,” “psychosis AND antipsychotics psychotherapy augmentation,” “medical resistance AND psychosis psychotherapy,” “treatment resistant OR treatment-resistant OR treatment resistance OR treatment-resistance AND psychosis AND/OR schizophrenia AND psychotherapy AND/OR psychodynamic psychotherapy AND/OR therapeutic relationship.” RCT, meta-analyses relevant open-label trials, significant articles, including case reports, controlled and uncontrolled trials, and ongoing trials of pharmacological treatments, augmented or substituted with psychotherapeutic approaches to TRP and TRS, have been selected. No language restriction was applied, and relevant cross-references were retrieved as necessary. Studies concerning augmentation or
substitution with medication have been excluded. Articles referring to TR in different pathologies from nonaffective psychosis and schizophrenia spectrum disorders have also been excluded. To overcome the problem of nonspecificity in psychotherapy, particular attention has been paid to the psychotherapy method and its details and to the control groups. Critical and systematic reviews on psychological interventions in TRP and TRS have been considered for a further review of literature. The most frequent cluster of symptoms measured by clinical scale assessments that have been included are 1) general psychopathology, 2) positive and negative symptoms, 3) cognitive symptoms, 4) affective symptoms, and 5) social functioning. The following aspects have been considered: 1) the stage of illness, such as the prodromal phase, the onset, any time after the onset and during the chronic phase; 2) the population of patients regarding diagnosis, duration of illness, age, age of onset, and duration of untreated psychosis (DUP); and 3) the type of psychotherapy, such as individual or group, duration of the treatment, frequency and time of the sessions, type of comparison or control group (if present), and blindmess of the raters.

About the meta-analysis portion, we performed a fixed-effect meta-analysis aimed at evaluating the efficacy of augmentation therapy with CBT in terms of variation of the total PANSS scores (see Figure 3). A further meta-analytical random-effect evaluation was carried out in order to evaluate the effectiveness of augmentation therapy with CBT in terms of variation of the total PANSS scores (see Figure 4). The estimate uses SMD (standard mean difference pre- vs. posttreatment) as an effect size.

The heterogeneity index of the studies and the publication bias were respectively evaluated with $I^2$ and Funnel plots (see Figures 5, 6, and 7).

The inclusion criteria used for the selection of the RCTs suitable for the meta-analysis carried out were as follows:

1. Presence of a uniform control group (patients treated with the usual therapy) (TAU)
2. Measurement of outcome with validated scales (PANSS)
3. Studies only of the RCT type
4. Same type of psychotherapeutic intervention (individual CBT)
5. Evaluation, pre- and posttreatment, with the same type of scale
6. Follow-up to 6 or 9 months

**Study Selection**

Included papers were those reporting efficacy outcomes about the positive and/or negative symptoms of TRS and TRP exposed to antipsychotic replacement or augmentative psychotherapy, any modality. Outcome measures could be reordered by means of varying standard rating tools or by means of the clinicians’ judgment.
Data Collection Process
Two authors (DP and MP) conducted a two-step literature search, examining all titles and abstracts, accessing the full texts of potentially relevant papers. Upon data collection and extraction, the appointed authors compared their results with each other to reach a final consensus based on consensual inclusion and exclusion criteria. Any eventual discrepancy between the principal investigators, blind to each other, was solved by consultation with the senior author (AdB). Finally, the leading senior author with considerable experience on the topic (AdB) assisted in manuscript revision. Data were sought for the following characteristics: participants, interventions, comparisons, outcomes, and study design (PICOS), as well as funding sources. Specifically, the recorded variables for each article included in the review were the following: author(s), year of publication, study design, sample size, eventual follow-up or control group, outcome measures, conclusions, limitations, quality score, and quality differentiation.

Risk of Bias in Individual Studies
Potential major confounding biases in the studies were ascertained at study level focusing on the following: measurement/diagnostic bias (e.g., lack of reliable diagnostic tools to make the diagnosis of TRS or TRP), confounding bias (e.g., lack of stratification and multivariate control for specific sociodemographic, vital, or clinical features), information (especially recall) bias, unrepresentativeness or inhomogeneity of the sample size or lack of control group (where applicable),

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**FIGURE 2** | Meta-analysis of PANSS positive symptoms.

**FIGURE 3** | Meta-analysis of PANSS negative symptoms.
and selection by indication bias (nonrandom assignment of the exposure where applicable) (111).

**Scoring and Ranking of the Studies**
The present systematic review purposely encompassed a broad range of records and different types of study designs. To avoid an “apples and oranges” bias, we strived at stratifying the appraised results by discriminating between different quality levels. Specifically, observational case–control reports were appraised by means of the Newcastle–Ottawa Rating Scale (see Table 1) (118) and randomized controlled studies were appraised using the Jadad scale (see Appendix 1) (119).

**Risk of Bias Across the Studies**
Any eventual bias affecting cumulative evidence (e.g., publication bias, selective reporting within studies) was assessed through the study evaluation process and accounted in the discussion of the present manuscript.

**RESULTS**
The process of the literature search is shown in Figure 1. The search identified 42 references, of which 18 were RCT articles (see Table 2 for all the types of studies). Appendix 1 provides an overview of descriptive information about the 42 studies.
Overall Number, Selected Number, and Typology of Psychotherapy Intervention

Only patients who had been stable on medication for a defined period (from 8 weeks to 6 months) were included in the studies. As reported in Table 3, CBT works were found in 32 trials: 25 on individual and 7 on group CBT. Social skill training (SST) was studied in adjunction to CBT, and they were compared to supportive counseling (SC) in one trial (120). Works on family interventions (FI), psychosocial intervention (PI), psychoeducation (PE), key-person counseling (KC), cognitive remediation (CR), supportive counseling (SC), and supportive therapy (ST) were studied in comparison with CBT in 12 CBT works. No studies with these interventions alone on TRP patients have been found. In one trial, CBT was compared to SC plus PE (121). Mindfulness was used in adjunction to CBT, acceptance-based intervention (ACT), and treatment of resistant command hallucinations (TORCH) in one study (122), while it was examined alone in another work (123). One study on multimodal individual psychotherapy, including individual CBT, was found (114). Two controlled trials that compared individual CBT to treatment as usual (TAU) have been collected (117, 124). One RCT that compared CBT to enriched TAU (125) has been found. The studies regarding other interventions alone were as follows: reasoning training (RT, n = 2) (112, 126), metacognitive therapy (MCT, n = 2) (127), cognitive therapy for command hallucinations (CTCH, n = 1) (128), art group

FIGURE 6 | Funnel plot of PANSS negative symptoms.

FIGURE 7 | Funnel plot of PANSS total.
therapy ($n = 1$) (129), occupational therapy (OT, $n = 1$) (130), and psychodynamic-interpersonal therapy (PIT, $n = 1$) (131).

Ten of the 42 studies regarded group therapy ($n = 1$) (129), occupational therapy (OT, $n = 1$) (130), and psychodynamic-interpersonal therapy (PIT, $n = 1$) (131).

The CBT studies represented the majority of articles (32 out of 42). They were generally rigorous, as 22 out of 32 were of the RCT type, including 3 follow-up studies and 2 meta-analyses, while 10 studies included six trials with a control group. Only four CBT studies had no comparison group or control group. Some CBT researchers have used befriending (BF) (122, 139, 140). An RCT study on BF in first episode psychosis has been found and reported in Appendix 2 (64). The mindfulness study used BF as a comparison group as well. The work on multimodal psychotherapy used a TAU control group. Of the remaining studies, 3 out of 9 included a control group: the brief RT was compared to the Attention Control Activity (141). OT was compared to clozapine alone (130), and the CTCH was compared to TAU (128).

Moreover, a meta-analysis (138) was focused on individual and group FI studies on schizophrenia patients who were both TR and not TR patients and included CBT works in TRS patients, who were accurately described.

For this reason, it has been incorporated in our work. A second phase of the same meta-analysis has been excluded, as it did not pertain to medication resistance (142). The dose of treatment was measured by the total number of sessions and was from 4 to 27, given throughout a period between 12 weeks and 24 months. In five studies, the number of sessions and the time of treatment were not specified.

### Therapists and Blindness

Therapists were generally expert, except for one case (143). In two cases, the raters were trained and experienced nurses (140, 141). One study specifically on treatment resistance in early psychosis was found (144). Another study included early psychosis in a heterogeneous group (93). Eighteen articles were trials with blind raters, while blindness could not be used in 21 works. Only one meta-analysis out of three was specifically focused on blind studies (145). The Cochrane review compared blind studies with nonblind studies (146).

### Stage of Illness

The stage of illness (initial or chronic) was heterogeneous in 10 studies, where the patients who were enrolled had different ages or very diverse duration of illness. In 11 articles, the duration of
illness was not specified. Twenty trials had a sample of chronic TRP patients. None of the found articles resulted in reporting the DUP.

Pharmacological Co-Treatment
In only two studies were there patients who were not on medication. In the first, there were 5 of 40 patients in an uncontrolled naturalistic study of CBT plus FI (147), while in the second there were 3 of 12 patients on individual CBT in a RCT (148). Remarkably, no study has proposed a psychological treatment as an alternative to medication in the whole sample. No study with regard to music therapy, specifically on medication-resistant psychosis patients, has been found. However, other 18 studies, which did not focus on TR patients and were not included in this research, have been collected in Appendix 2.

Clinical Outcome
Assessments used to measure improvement often differed between the various trials. Hence, we pooled study results either based or not based on statistics along with the authors’ conclusion to compare them. See Table 4 for details on the number of works that had statistically significant outcomes. Articles reporting no improvement are also included in Table 4. No changes after treatment have been observed in only 2 studies out of 42. Those two trials were on CBT: one on CBT integrated with FI (147) and one on group CBT (132).

Symptoms and Clinical Domains
The symptomatology studied in the retrieved trials is mainly represented by the positive symptoms and, above all, the auditory hallucinations, especially in the CBT studies, while negative symptoms have been rarely evaluated. Ten studies out of 42 reported a decrease of negative symptomatology (see Table 4). Efficacy on negative symptoms has been shown in three CBT trials and in ST, CR, CTC, and OT. Art group therapy, MCT, and PIT trials have also reported a positive outcome on negative symptoms but without control group and not statistically evaluated (see Appendix 1 and Table 4). Affectivity has not been specifically evaluated, except for art group therapy and PIT. Clinical progress has also been observed in other areas, such as social functioning and personal care. Self-esteem and hopelessness have been evaluated, but their improvement has not been shown.

Studies with chronic patients affected by treatment resistance have shown that CBT could be effective, providing positive symptom reduction, which was considered equivalent to a “medium effect size.” A trend to effective treatment has been observed as well, in case series with psychosis onset, which was resistant to medication alone: almost three-quarters of patients achieved clinically significant improvement (144). However, results of CBT efficacy compared to other treatments in TRP are not homogeneous in all studies. For instance, when compared to other treatments, similar improvements to the CBT experimental group have been observed in other comparison groups, while a significant difference has been constantly observed only from TAU (132). In particular, in the Cochrane meta-analytical review on schizophrenia including TRS, psychosocial therapies have shown no clear difference from CBT for outcomes relevant to adverse effect/events, global mental state measures, and effects on positive or negative

| Psychological intervention on TRP patients | Studies with statistically significant improvement | Studies with no statistically significant improvement | Studies with no different improvement between groups | Studies with no improvement | Studies with improvement specifically on negative symptoms |
|------------------------------------------|-----------------------------------------------|-----------------------------------------------|-------------------------------------------------|----------------------------|-----------------------------|
| Individual CBT                           | 8                                             | 2                                             | 0                                               | 0                          | 2                           |
| Individual CBT vs. Befriending            | 1                                             | 0                                             | 0                                               | 0                          | 1                           |
| Group CBT                                | 3                                             | 0                                             | 0                                               | 0                          | 0                           |
| Group CBT vs. Group ST                    | 1                                             | 0                                             | 1                                               | 0                          | 0                           |
| CBT vs. Psychosocial Intervention         | 0                                             | 0                                             | 1                                               | 0                          | 0                           |
| CBT, Supportive Therapy                   | 0                                             | 0                                             | 1                                               | 0                          | 0                           |
| CBT vs. Psychoeducation                   | 0                                             | 0                                             | 2                                               | 0                          | 1                           |
| CBT vs. Supportive Counseling             | 2                                             | 0                                             | 3                                               | 0                          | 0                           |
| CBT, Family Intervention                  | 1                                             | 0                                             | 0                                               | 1                          | 0                           |
| CBT, Social Skill Training vs. ST         | 0                                             | 0                                             | 1                                               | 0                          | 0                           |
| CBT, ACT, TORCHi, Mindfulness vs. Befriending | 0                                             | 0                                             | 1                                               | 0                          | 0                           |
| CBT vs. Cognitive Remediation             | 0                                             | 0                                             | 1                                               | 0                          | 0                           |
| Multimodal Psychotherapy                  | 1                                             | 0                                             | 0                                               | 0                          | 0                           |
| Reasoning Training                        | 1                                             | 1                                             | 0                                               | 0                          | 1                           |
| Cognitive Therapy for Command Hallucinations (CTCH) | 1                                             | 0                                             | 0                                               | 0                          | 1                           |
| Mindfulness                              | 0                                             | 1                                             | 0                                               | 0                          | 0                           |
| Metacognitive Therapy                     | 2                                             | 0                                             | 0                                               | 0                          | 0                           |
| Art Group Therapy                         | 0                                             | 1                                             | 0                                               | 0                          | 0                           |
| Occupational Therapy                      | 1                                             | 0                                             | 0                                               | 0                          | 1                           |
| Psychodynamic Interpersonal Therapy       | 0                                             | 1                                             | 0                                               | 0                          | 1                           |
| Total                                    | 22                                            | 6                                             | 12                                              | 2                          | 10                          |
symptoms (146). Moreover, the studies comparing CBT to another treatment, such as cognitive remediation (149), befriending (122, 140), supportive therapy (115, 120, 134), psychoeducation (113, 150), supportive counseling (121), or family intervention (138), have shown significant clinical improvement in all groups that were studied. Finally, a statistically significant major improvement in supportive therapy has also been observed (135). Two trials have shown a significant improvement in the CBT group when compared to other psychological interventions, such as befriending (139) or supportive counseling (151). Moreover, in two follow-up studies, CBT did not maintain the superiority to SC (152, 153). In particular, after 1 year from the end of treatment, CBT started to decline while SC improved, and this trend continued at 2-year-follow-up. Finally, our results show that group therapy is related to significant improvement for all psychological interventions retrieved, except for family intervention (138), where single family treatment resulted better than the group family one. In six out of seven trials, group CBT presented the same improvement as the comparison group, showing the same results that were observed in the studies on individual CBT.

Meta-Analysis Result
The results obtained in our meta-analysis concerning the domain “POSITIVE SYMPTOMS” of the PANSS scale are as follows:

Fixed-effect meta-analysis: number of studies = 4; number of comparisons (k) = 4; total sample = 800 patients; SMD (standard mean difference) = 0.237 (C.I. = 0.097–0.376).

These preliminary results suggest that, on average, the PANSS score for positive symptoms was reduced by 23.7% more (with a margin between 9.7% and 37.6%) in patients who performed augmentation therapy with CBT compared to patients who received the usual therapy (TAU) (see Figure 2). Moreover, this reduction is statistically significant (p = 0.001).

Although the number of meta-analyzable studies is small, the heterogeneity index I² is 0% (Figure 5).

The results obtained in our meta-analysis concerning the domain “NEGATIVE SYMPTOMS” of the PANSS scale are as follows:

Fixed-effect meta-analysis: no. of studies = 4; number of comparisons (k) = 4; total sample = 800 patients; SMD (standard mean difference) = 0.075 (C.I. = −0.063–0.214).

These preliminary results suggest that, on average, the PANSS score for negative symptoms was reduced by 7.5% more (with a margin between −6.3% and 21.4%) in patients undergoing augmentation therapy with CBT compared to patients receiving the usual therapy (TAU) (see Figure 3). However, this reduction is not statistically significant (p = 0.286).

Furthermore, it is noteworthy that the “lower limit” of the negative confidence interval (−6.3%) indicates how, at least in a small number of events, the CBT in augmentation to the usual treatment (TAU) could potentially induce even an effect opposite to the therapeutic one.

Although the number of meta-analyzable studies is small, the heterogeneity index I² is also 0% in this case (Figure 6).

The results obtained in our meta-analysis concerning the “TOTAL Score” domain of the PANSS scale are as follows:

Random-effect meta-analysis: no. of studies = 5; number of comparisons (k) = 5; total sample = 843 patients; SMD (standard mean difference) = 0.220 (C.I. = 0.443–0.004).

These preliminary results suggest that, on average, the total score at the PANSS was reduced by 22% more (with a margin between 44.3% and −0.4%) in patients who performed augmentation therapy with CBT compared to patients who received the usual therapy (TAU) (see Figure 4). However, this result is not statistically significant (p = 0.054).

Moreover, in this case, the heterogeneity index I² is equal to 46% and, being quite high, therefore indicates a poor homogeneity of the analyzed data (Figure 7).

DISCUSSION
Psychological Interventions
Psychological interventions in TRP patients have shown a therapeutic effect in 40 out of 42 selected studies. In particular, results demonstrate improvement in positive symptoms for CBT, as well as for other psychological interventions, albeit with different degrees. More specifically, CBT effects in selected studies were not statistically different respectively from psychosocial intervention (146), cognitive remediation (149), befriending (122, 140), supportive therapy (115, 120, 134, 135), psychoeducation (113, 150), supportive counseling (121), and family intervention (138).

CBT has been recognized as more efficient in persistent positive symptoms at follow-up. Supportive counseling (SC) was less effective than CBT at the 9-month follow-up, while it demonstrated the same efficacy as CBT at the following follow-up. Finally, the SC showed its superiority in some measures at 2 years follow-up (140, 153). It has been speculated that supportive counseling may enhance frequent and regular non-threatening social interaction, which might have worked on self-esteem and helped patients to recuperate their social activity (16). Furthermore, metacognitive therapy has also shown significant improvements in both positive and negative symptoms compared to the baseline (but a control group was not provided) (127). Although art therapy is not strictly considered as a form psychotherapy, it has shown to lead to improvements in a short time in fields that are not easily measured by regular assessments, for example when considering interpersonal relationship (129). Moreover, affectivity has not been specifically evaluated, except for art group therapy and psychodynamic interpersonal therapy (131), which were case series. In this work, clinical progress has also been observed in other areas such as social functioning, showing a marked reduction in the severe disturbances presented prior to treatment (131). Occupational therapy has been shown to give a statistically significant improvement compared to clozapine alone in the performance of the activity, in psychotic symptoms, social interaction, and personal care (130). Multimodal psychotherapy, reasoning training, and cognitive therapy for command hallucinations (CTCH) have also shown significant improvements compared to TAU (112, 114, 126, 128). The sample population targeted in the trials included different phases of the illness, showing
that an integrated treatment with psychological intervention and pharmacological treatment could be helpful at any point of the disease trajectory. On the contrary, no data on the use of psychological intervention alone on TRP patients are currently available.

Few methodological issues need to be considered, such as the type of intervention, characteristics of the sample, including age of patients as well as stage of the illness, and duration of the treatment. With regard to the type of intervention, it has already been observed that all psychological therapies, including befriending and supportive therapy, may have a clinically relevant impact, and statistically significant results are reported in more than half of the trials included in this review (22 out of 42, see Table 4).

A controversial aspect of psychotherapeutic interventions in TRP is represented by the fact that psychological interventions, including CBT, have an effect mainly on positive symptoms while they seem to be less clearly effective on other main aspects, such as negative and cognitive symptoms. Eighteen CBT trials have shown that CBT, in adjunction to antipsychotics, could produce better outcomes on a variety of measures than medication alone, but target treatment was mainly represented by positive symptoms. In fact, negative symptoms are generally left aside and remained prevalently persistent in the majority of studies. In some trials, negative symptoms have not even been evaluated. In summary, 10 studies out of 42 reported a significant reduction of negative symptomatology: 3 on CBT, 1 on CR, 1 on MCT, 1 on CTCH, 2 on occupational therapy, 1 on art group therapy, and 1 on psychodynamic interpersonal therapy (see Table 4). These evidence are also compatible with the result of a recent meta-analysis on psychological treatments of negative symptoms in a population of psychotic patients that were not specifically resistant to treatment (154). In particular, improvement in negative symptoms has been observed after CBT intervention in patients who were at any stage of the disease. This amelioration has resulted in 59% of the studies when CBT was compared to TAU, while none of the analyzed studies suggested a benefit of CBT if compared to active controls. Moreover, another recent meta-analysis for a total of 4,068 patients who were on average moderately ill at baseline has confirmed the efficacy of CBT on positive symptomatology (155). A recent systematic review has newly reported that CR can also have beneficial effects on negative symptoms, compared to TAU and TAU plus active control in schizophrenia patients who were not treatment resistant (68).

Additional researches are needed in order to test “self-disturbance” (156, 157). Consequently, it would be necessary “to tailor” psychological treatment aimed at this symptom. Since the “hyporeflexive attitude” is typical in self-disturbance and in nonaffective psychosis, CBT might not be the most suited psychological intervention on these patients. This is due to the fact that an important feature of this therapeutic approach is the encouragement of “thinking about thinking” (14, 158), which is what the patients already do repeatedly in a pathological fashion (159).

It has been observed that brain dysfunctions, for example, dopaminergic supersensitivity, could be secondary to psychological events (74, 160). Furthermore, studies on brain receptor availability after psychotherapy treatments (both CBT and psychodynamic psychotherapy) have shown that a neurobiological alteration can be modifiable or reversible thanks to psychological interventions (161–164). Further steps in augmentation with psychological therapy of TRP seem to be focusing on the total symptomatology, including positive, negative, and self-disturbance. Considering that symptoms are part of unitary and complex psychopathology, acting on one aspect could be partial. On the other hand, publications on psychodynamic psychotherapy, which is focused on unconscious dimension, are poorly available; only one paper referring specifically to TRP patients has been found in this review (131).

Other critical points are as follows: the characteristics of the sample, age of patients, stage of illness, and duration of the treatment. Some gaps have to be highlighted. Firstly, a marked heterogeneity of the selected sample has been observed in 10 trials, while 11 studies did not take it into account. For instance, patients at different ages or at different stages of illness (early stage, acute or chronic stage) were referred to nonpsychotic patients. A short-term duration of treatment was 12 months. In two studies, therapy was administered in 4 weeks, and in one study (147), the length of intervention ranged from 4 weeks to 9 months. Only 2 studies out of 42 (114, 138) used a duration of treatment up to 21–24 months, and in one study (147), the length of intervention was 12 months. In two studies, therapy was administered in one single session (112, 126), and in four trials, duration of treatment was not even specified. A significant recovery could not be expected during a 2-month treatment period, when patients are markedly ill and/or chronic with persistent and expressed negative symptoms of schizophrenia (129). This is supported by the observations of an increased effect over time of CBT on mental state (140). For instance, in the selected articles, a longer duration of treatment can generally show better results on negative symptoms. On the other hand, recent publications on the comparison between short- and long-term psychotherapy have shown contrasting results (167, 168). However, these works were referred to nonpsychotic patients. A short-term duration is insufficient for psychotic onset patients, who need to be treated longer, considering guidelines (169). Finally, according to our results, as reported in Table 5, group therapy should also be encouraged, as it is generally well supported by evidence in
improving persistent positive symptom in both CBT and other psychological interventions.

Exploratory Meta-Analysis of Cognitive Behavioral Therapy Interventions

The results obtained from our meta-analytical extraction have confirmed that cognitive–behavioral psychotherapy is very effective particularly in the treatment of positive symptoms in TRS and/or TRP patients. This result is in line with what has already been found in other studies in the literature. The same efficacy was not found in the treatment of negative symptoms while it was only partial in achieving an improvement in the total scores of patients evaluated in the PANSS. We have also found that CBT in augmentation with the usual treatment (TAU) works well in the initial stages and then gradually loses effectiveness (170). In this regard, we can hypothesize that schizophrenia worsens over time, making treatment with CBT more difficult and therefore less effective; moreover, it could happen that, in the initial stages of treatment, there is a sort of “feeling of well-being” that does not necessarily coincide with a real clinical improvement. However, there are very few studies with a sufficiently long follow-up to clarify these hypotheses. As regards the low incisiveness of CBT on negative symptoms, we can hypothesize that patients with more pronounced negative symptoms and therefore with affective dullness and social withdrawal are less suitable for this type of psychotherapeutic approach or that these symptoms require a longer duration of treatment to be effectively affected. Moreover, given that the few studies in the literature with a longer follow-up have shown an efficacy also on the negative symptoms, we can hypothesize that the patients followed for a longer period may have benefited from therapeutic adjustments over time as well as from the CBT. The limits of these results are in some way superimposable to those already listed above about the systematic review on the same topic. In addition to what has already been said, the incompleteness and the partiality of the data at our disposal are worth noting, as, for example, not all the articles indicated the dropout rates accurately, or at what time of the treatment they occurred, or which group they belonged to (cases or controls).

### CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

Psychotherapy should be considered a potential relevant therapeutic strategy in conjunction with medication in TRP patients. An intervention on psychosis that does not consider an integrative approach could miss a potential effective component of the treatment. However, few questions need to be addressed in the future in order to better understand the role of psychotherapy in TRP. Firstly, it would be appropriate to start with large-scale multicenter, controlled studies based on psychotherapeutic approaches (i.e., CBT) that were shown to be effective in smaller studies and to include patients with homogeneous domains of symptoms, duration and doses of antipsychotic treatment, as well as duration of illness. Secondly, a longer time of treatment should be conceived in such studies in order to get an adequate signal of the response. Finally, even if challenging, an important issue is to consider the inclusion of biological markers (i.e., functional imaging) before and after the introduction of the psychotherapeutic augmentation or of the substitution psychotherapy. Moreover, future studies need to adopt reliable operational outcome measures for non-CBT studies to allow quantitative extraction of information and reliable comparison of efficacy measures for psychological interventions other than cognitive therapy that are currently almost invariably not assessed in a controlled, RCT fashion.

### AUTHOR CONTRIBUTIONS

DP designed the study, searched the database, wrote the article, and created the appendices, tables, and figures. MP searched the database and participated in the editing of the manuscript. MP and VD supervised the literature procedure extraction, commented on the last draft, and contributed to the writing of the manuscript. AdB wrote and commented the manuscript, and contributed to the writing of the manuscript. MF and VD supervised the literature procedure extraction, commented on the last draft, and contributed to the writing of the manuscript. AUTHOR CONTRIBUTIONS

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### APPENDIX 1

| Author/type of study | Psychological intervention | Adjunction/antipsychotic | Number of patients/comparison groups | Stage of illness/age of patients/diagnosis | Frequency (and time) of sessions/duration of treatment | Results | Jadad score |
|----------------------|---------------------------|--------------------------|---------------------------------------|---------------------------------------------|-----------------------------------------------------|--------|------------|
| Morrison et al. (171) | Metacognitive therapy (MCT) | Yes/atypical             | 10 patients MCT/none                  | Not specified/34.3 years/ schizophrenia (SKP), schizoaffective disorder (SKA), delusional disorder (DD), other* | 6–12 sessions/9 months                               | PANSS total and positive significantly reduced at the end of treatment (E) and at 3 months follow-up (FU); PSYRATS reduction with borderline significance | – |
| Hutton et al. (127)  | MCT                        | Yes/Various              | 3 patients MCT/none                   | Chronic SKP/15, 20, and 40 years/KA, DD, with positive symptoms | 11–13 1-h weekly sessions/3 months                    | Clinical worthwhile benefits in all. In 2 patients, significant PANSS reduction and increased recovery. At 3 months, FU reduction in positive and negative symptoms | – |
| Birchwood et al. (93) | Individual CBT for command hallucinations | Yes/atypical             | 98 patients CBT+ Treatment as usual (TAU)/99 TAU | Heterogeneous/≥16 years/ SKP, SKA, psychosis (P), bipolar disorder (BD), with self-harm | Up to 25 sessions/9 months                          | Reduction of compliance to voices but not significant | 3 |
| Burns et al. (145)   | Individual CBT             | Yes/Various              | 552 patients/waiting list, TAU/other | Not specified/not specified/ SKP, SKA, DD | 10–24 sessions/6 weeks to 9 months                   | Statistically significant beneficial effects of CBT at E and FU for positive and general symptoms | – |
| Jones et al. (132)   | CBT vs. other psychosocial therapies | Yes/Various              | Not specified; 20 trials/CBT/psychosocial therapies/TAU | Heterogeneous/18–65 years/ SKP | Various                                              | No advantage for CBT over other treatments, including less sophisticated therapies | – |
| Mandi–Gajić G (129)  | Group art therapy          | Yes/Various              | 2 patients/no control group           | Chronic, 31 years, 27 years/ paranoid and simplex SKP with severe negative symptoms | Not specified/2 months                               | Improvement in all symptoms, but not statistically significant; Intervention has helped to understand the inner world of patients | – |
| Klingberg et al. (149) | Individual CBT, cognitive remediation (CR) | Yes/not specified        | 99 CBT+TAU/99 CR+TAU                  | Chronic/18–55 years/ SKP, outpatients at least with moderate negative symptom | 16.6+ CBT sessions vs. 13.7+ OR sessions/9 months | No suicide, at the E and at 3 months FU adverse events (AEs) in 10 CBT patients, including suicidal attempts, and in 5 OR patients. Depression more frequent in CBT patients. Not statistically significant results | 3 |

(Continued)
| Author/type of study | Psychological intervention | Adjunction/antipsychotic | Number of patients/comparison groups | Stage of illness/age of patients/diagnosis | Frequency (and time) of sessions/duration of treatment | Results | Jadad score |
|----------------------|---------------------------|--------------------------|--------------------------------------|--------------------------------------------|------------------------------------------------------|---------|-------------|
| Shawyer et al. (122) | CBT with acceptance-based intervention (ACT), treatment of resistant command hallucinations (TORCH), mindfulness, befriending (BF) | Yes/not specified | 21 CBT/21 CBT/22 BF/17 control group (waiting list) | Chronic/18–65 years; 59 years+/SKF (72%), SKA (21%) and affective P (7%) | 1,550 min weekly sessions/4–6 months. 10 minutes mindfulness exercises, with home practice | Subjective greater improvement in CBT vs. BF, but not significant results. CBT here has more modest effect that in early studies | 4 |
| Waller et al. (126) | Reasoning training, Maudley review training program | Yes/not specified | 13 patients/no control group | Chronic/44.6 years (mean)/P with low levels of belief flexibility, with jump to conclusion | Single session. One-off computerized training package, lasting approximately 1.5 h | Significant improvement at post-intervention in belief flexibility and improved reasoning | – |
| Eidsdon (144) | Individual CBT | Yes/according to the early psychosis program | 14 patients/no control group | Early psychosis patient/≥18 years/SKP spectrum outpatient | 15–25 sessions/not specified period | Significant reduction of positive symptoms and not significant reduction of PANSS negative scale | – |
| Peters et al. (143) | CBT by nonexpert therapists (supervised) | Yes/vegetarian; unmedicated: 6% in the therapy group, 3% in the control group | 36 CBT (in 2 CBT groups)/38 TAU | Not specified/18–65 years/P with persistent positive symptoms | 16 (mean) weekly or fortnightly sessions lasting up to 1 h/6 months | Significant main result in depression, in CBT. At PANSS, positive improvement only in one CBT group | 3 |
| Jacobsen et al. (109) | Mindfulness Group | Yes/Not specified | 8 patients>No control group | Chronic/21–43 years/Complex Psychosis inpatients | 1-hour weekly session with 3–5 people/6 weeks | Improvements in PSYRATS, SMQ and a stress scale, but a statistical analysis of results was not provided | – |
| de Paiva Barretto EM et al. (139) | Individual CBT, befriending (BF) | Yes/clozapine | 12 CBT/9 BF | Chronic (CBT 15+/years, BF 10+/years)/CBT 39.8+/SKP 43.2+/TRS | 20 sessions/21 weeks | Statistically significant improvement in positive symptoms in CBT. Reduced negative symptoms in both groups but not significant | 1 |
| Penn et al. (135) | Group CBT/group supportive therapy (ST) | Yes/At least two trials, one atypical for 8 weeks prior to randomization | 32 group CBT/33 group ST | Non specified/18–65 years/SKP or SKA outpatients | Twelve 1-h weekly CBT sessions/3 months; 12 weeks of enhanced ST (172) | Statistically significant improvement only in ST group at E. At 12 months FU significant reduction also in CBT group at PANSS. ST had more specific impact on hallucinations | 4 |
| Brabban et al. (141) | Brief CBT | Yes/not specified | 226 CBT/128 TAU | Not specified/CBT40+, TAU 41.2+/SKP | From three to six 1-h sessions/2–3 months | Improvement, but not significant | 3 |

(Continued)
| Author/type of study | Psychological intervention | Adjunction/antipsychotic | Number of patients/comparison groups | Stage of illness/age of patients/diagnosis | Frequency (and time) of sessions/duration of treatment | Results | Jadad score |
|----------------------|---------------------------|-------------------------|--------------------------------------|-------------------------------------------|------------------------------------------------------|--------|------------|
| Ross et al. (112)    | Reasoning training (RT), attention control activity (ACA) | Yes/not specified | 1st stage: 34 RT/34 healthy volunteer 2nd stage: 17 RT/17 ACA | Chronic/16.2 years+RT, 10.8 years+ controls/SKP spectrum disorder | 45-min reasoning intervention in 3 tasks | After training, 24% showed greater belief flexibility and 18% showed a reduction in delusional conviction. Not statistically significant. | – |
| Johnson et al. (134) | Group CBT/Group ST | Yes/2 trials, one of which atypical for 8 weeks | 58 patients randomly assigned to either group | Chronic/42.1 years/SKP; SKA outpatients | Twelve 1-h weekly sessions, 1–2 therapists for 4–7 patients over 12 weeks | No difference in ratings between groups. | 3 |
| Barrowclough et al. (132) | Group CBT | Yes/not specified | 12 patients CBT group/12 TAU | Not specified/age of illness: 13.67++ years; 18–55+ years/SKP | 18 sessions of 2 h including breaks over 6 months | No difference between groups at PANSS, SFS, HADS, BHS, RSE, GAF | 1 |
| Cather et al. (113)  | Functional CBT (CBT), psychoeducation (PE) | Yes/diazepam | 1.5 CBT/15 psychoeducation (PE) | Not specified/age of illness: 24.88++ years; 18–66+ years/SKP, SKA | 16 weekly sessions over 4 months | Greater benefit for CBT on positive symptoms at PSYRATS voices subscale. Not statistically significant | – |
| Zimmermann et al. (173) | CBT mainly individual | Yes/various | 1,484 patients in 14 studies with at least one CBT group with a control group | Heterogeneous; 10 studies on chronic condition and TRP plus 3 studies on acute; 36.02+ years/SKP spectrum | Weekly sessions/5 weeks to 9 months | Significant reduction of positive symptoms in CBT | – |
| Wykes et al. (137)   | Group CBT | Yes/typical and atypical antipsychotic | 4.5 CBT/TAU/40 TAU (10 people had specific individual psychotherapy, contaminating the sample) | Chronic/39.7 years/SKP | Seven sessions/10 weeks | Significant improvement for group CBT patients in social functioning at FU. (Effects could be influenced by extra psychological help and change of medication). No improvement in the severity at PSYRATS | 4 |
| Valmaggia et al. (121) | Individual CBT supportive counseling (SC) plus psychoeducation (PE) | Yes/atypical antipsychotic | 36 CBT/26 SC, PE | Chronic/18–70+ years/TRS | 16 1-h sessions; 12 weekly sessions, 3 fortnightly sessions and last session after 4 weeks/22 weeks | No significant differences between the group at PANNS and PSYRATS, except for the factor 2 of the hallucination subscale | 2 |
| Pinkham et al. (136) | Group CBT | Yes/atypical antipsychotics | 11 patients in two CBT groups/ No control | Chronic/39.6 years/SKP; SKA inpatients | 1-h weekly sessions/7 weeks, 11 weeks | Significant changes in both groups in the participants’ beliefs | – |
Continued

| Author/type of study | Psychological intervention | Adjunction/antipsychotic | Number of patients/comparison groups | Stage of illness/age of patients/diagnosis | Frequency (and time) of sessions/duration of treatment | Results | Jadad score |
|----------------------|---------------------------|--------------------------|--------------------------------------|------------------------------------------|------------------------------------------------------|---------|-------------|
| Trower et al. (129)  | Cognitive therapy for command hallucinations (CTOH) | Yes/typical or atypical | 18 CBT/TAU/20 TAU | Heterogeneous; 17–40+ years/SK&P spectrum disorder with “severe commands” | On average 16 sessions/6 months | Significant reduction of the compliance with voices with maintained results at 12 months FU. Small reduction in negative symptoms | 4 |
| Temple and Ho (124) | Individual CBT | Yes/not specified | 8 CBT/9 TAU | Not specified. Age of illness onset 21+ years CBT; 24.2+ TAU; 28.8+ years CBT; 35.9+ years TAU/SKP | 19–30 sessions/not specified timing and frequency | CBT showed a statistically significant decline in delusions and hallucinations. Trend of reduction in negative symptoms (p = 0.06) | – |
| Randal et al. (114) | Individual multimodal psychotherapy (individual, flexible and recovery-focused) | Yes/minimum dose of atypical antipsychotics | 9 Multimodal psychotherapy + TAU/12 TAU group retrospectively considered | Chronic/age of onset 18.9–19.3 years; duration of illness 8.6–11.2 years; 29–30+ years/SKP; SKA inpatients (rehabilitation) | 15 min to 1 h, twice weekly reduced to weekly and to fortnightly or monthly/ up to 21 months | Clinically significant improvements in the overall PANSS, as well as scores for deviant behavioral ROS | – |
| Rector et al. (125) | Individual CBT + ETAU (enriched TAU) | Yes/typical, atypical antipsychotic, anti depressants | 24 CBT + ETAU/18 ETAU | Chronic/age of onset 21+ CBT/ETAU; 19.2+ ETAU; 37.5+ years CBT/ETAU; 41.2+ ETAU/SKP | 20 sessions/6 months | Significant effects for positive, negative, and overall symptom severity at E, but nonsignificant reduction of negative symptoms at 6 months FU | 4 |
| Durham et al. (115) | Individual CBT, supportive psychotherapy (SPT)+ | Yes/typical or atypical antipsychotics | 22 CBT/23 SPT + TAU/21 TAU | Chronic/duration of illness 15++ CBT; 14++ SPT; 10 TAU; 36+ years/SKP; SKA; DD | Up to 20 sessions of approximately 30 min/over 9 months | Significant improvement in CBT and SPT groups vs. TAU, at 3 months FU, but nonsignificant differences between CBT and SPT at E | – |
| Buchain et al. (130) | Occupational therapy | Yes/clozapine | 14 Occupational therapy/12 clozapine | Chronic/age of onset 20.9+ years; 19.67+ years; 33.71+ years; 36.58+ years/TRY | Nonspecified sessions/6 months | Statistically significant difference at EOITO | 2 |
| Pilling et al. (138) | Family intervention (FI) or CBT | Yes/variables | 1,467 of 18 FI trials/other treatments or TAU or no control group; 528 of 8 CBT studies/ several other treatments | Chronic/Duration of illness: 6 ± 5+ years FI, 11+ years CBT; 31.2+ years FI, 33.9 years CBT/SKP | 8 sessions over a short time period, fortnightly for 2 years, then monthly for 4 years for FI; weekly, monthly sessions 6 weeks to years for CBT | Significant benefit more in FI than standard care, nonsignificant when compared to other treatments More improvement in single FI than in group FI. CBT shows clear positive effects at 9 months FU | – |
| Author/type of study               | Psychological intervention                                                                 | Adjunction/antipsychotic                                                                 | Number of patients/comparison groups | Stage of illness/age of patients/diagnosis                                                                 | Frequency (and time) of sessions/duration of treatment | Results                                                                                                                                                                                                 | Jadad score |
|-----------------------------------|---------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-------------------------------------|----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| Wersma et al. (147)               | CBT and coping training in an integrated single family treatment program                      | Yes/typical (65%) or atypical (8%) antipsychotics, antidepressants, benzodiazepines, and/or other medication (17%); 5 patients used no medication at all | 40 patients/no control group        | Heterogeneous/duration of auditory hallucinations: 8+ years; 37+ years/SKP                                                                 | Average number of contacts 15 (varying from 2 to 51)/1–32 months                                      | Worsening or no improvements at PANSS. Subjective improvement at the end of the study and at 2 or 4 yearsFU in patients and family. Statistically significant reduction at <2 years, but not at 4 years. Disappearance of hallucination in 18% of patients. At discharge, 20% of the patients left without any antipsychotic medication. | –           |
| Tarrier et al. (153)              | CBT, SC Individual                                                                           | Yes/Various                                                                              | CBT/SC/TAU                          | At this FU, 61 out of 72 patients were available                                                                                           | See Tarrier et al. (151)                                                                                     | No significant differences. During the 2nd year, CBT continued to decline, whereas SC improved.                                                                                                       | –           |
| Sansky et al. (140) RCT            | CBT, befriending                                                                             | Yes/Various                                                                              | 46 CBT/44 BF                        | Chronic/duration of illness: 14–15+ years; 39–40+ years/SKP                                                                             | 18 45-min weekly sessions.9 months and less frequent after                                                  | Significant clinical improvement in both groups at E.                                                                                                                                                    | 3           |
| Davenport et al. (131)             | Interpersonal therapy (conversational, model of Hobson)                                      | Yes/Various                                                                              | 2 patients/no control group         | Chronic/onset at 18 years; F, 38 years; M, 43 years/SKP                                                                                   | Weekly community group, twice daily staff handover meetings                                              | Improvement at the Krawiecka Goldberg Vaughan scale for schizophrenia social behavior schedule.                                                                                                           | –           |
| Chadwick et al. (133)              | Group CBT                                                                                    | Yes/not specified                                                                        | 22 CBT no control group             | Not specified/SKP and SANS, TRP                                                                                                           | Eight 1-h weekly sessions over 8 weeks                                                                  | Significant improvement in mean conviction scores and in the three beliefs.                                                                                                                              | –           |
| Klingberg et al. (150)             | Psychosocial/medication management training (PMT), CBT                                       | Yes/Various                                                                              | 191 patients PMT/PMT+ CBT/PMT+ key person counseling KO/PMT+ CBT+KOC/TAU               | Chronic/age at onset 22.9+ years; 31.3+ years/SKP                                                                                         | 10 h of PMT combined with 15 h of CBT and with 15 h of KO/8 months                                         | Not significant difference in BPRS, SANS.                                                                                                                                                                    | –           |
### Author/type of study

| Author            | Type of study | Psychological intervention | Adjunction/antipsychotic | Number of patients/comparison groups | Stage of illness/age of patients/diagnosis | Frequency (and time) of sessions/duration of treatment | Results                                                                                     | Jadad score |
|-------------------|---------------|---------------------------|--------------------------|--------------------------------------|-------------------------------------------|--------------------------------------------------------|------------------------------------------------------------------------------------------------|------------|
| Pinto et al. (120) | RCT           | CBT, SST, ST              | Yes/clozapine            | 20 CBT + SST + clozapine/21 supportive therapy (ST) + clozapine | Not specified/duration of illness: 11.6–11.7++ years/33.9+ CBT, 35.8 ST/ SKP | 1-h weekly sessions/6 months. Monthly family support | Statistically significant improvement in both groups but no significant difference for negative symptoms. | 3          |
| Tarrier et al. (152) | RCT           | CBT, SC                   | Yes/various              | CBT/SC/RC                           | See Tarrier et al. (137)                     | See Tarrier et al. (137) | Significant difference in CBT vs. RC for positive symptoms. Nonsignificant improvement for negative symptoms | –          |
| Tarrier et al. (151) | RCT           | CBT, SC                   | Yes/typical and atypical antipsychotics | 33 intensive CBT+ routine care (RC)/26 SC + RC/28 RC | Heterogeneous/duration of illness: 11++ years; 38.6+ years/SKP, SKA, DD | Twenty sessions/10 weeks, 4 booster (B) sessions/4 months; 6 h SC session/10 weeks, 4 B sessions; 20 RC/10 weeks | Significant improvement for positive symptoms in CBT vs. SC and RC, and in SC vs. RC. RC showed slight deterioration. 18 patients achieved 50% improvement in psychotic symptoms. 11 CBT, 4 SC, 9RC | 3          |
| Levine et al. (116) | Controlled trial | Group CBT                  | Yes/typical antipsychotics | 6 group CBT/6 control group | Chronic; duration of illness: at least 5 years 20–45 years/paranoid SKP | Six 50-min weekly sessions, with a 4-week follow-up | Significant result at PANSS score at 4th and at 6th week and at 4 weeks follow-up in group CBT | –          |
| Kuipers et al. (148) | RCT           | Individual CBT            | Yes/various              | 2.8 of 60 CBT plus standard care/32 TAU | Heterogeneous/duration of illness: 12.1++ years CBT, 14++ years TAU; 38.5+, CBT, 41.8+ TAU/SKP, SKA, DD | Mean number of 1-h session (flexible)/15 given over 9 months | Significant improvement only in CBT group, who showed a 25% reduction on the BPRS. Three people became worse and one committed suicide | 3          |
| Gaetz et al. (117) | Controlled trial | Individual CBT            | Yes/not specified        | 13 CBT/7 TAU (waiting list group) | Chronic/duration of illness 16.5+ years CBT, 10.9+ years TAU; 39.6+ years CBT, 37.6+ years TAU/SKP or SKA | Weekly or fortnightly sessions, up to 22 sessions, with an average of 16 sessions/6 months | Significant improvement in delusions, preoccupation and action at MADS, BPRS in CBT group. No variations in self-esteem, distress, and insight. | –          |

* According to the entry criteria for an early intervention for psychosis service, defined using PANSS scores of at least 4 on hallucinations or delusions or at least 5 on conceptual disorganization, grandiosity, or suspiciousness, in the context of initial presentation to services with psychotic experiences.

+ Mean age of patients (yrs); ++ Mean duration of illness (yrs).
## APPENDIX 2

| Author/type of study                                      | Psychological intervention | Adjunction/antipsychotic | Number of patients/control group | Stage of illnesses and/or age of patients/diagnosis | Frequency and time sessions/duration of treatment | Results |
|----------------------------------------------------------|---------------------------|--------------------------|----------------------------------|-----------------------------------------------------|---------------------------------------------------|---------|
| Hutton, (174) Simple meta-analysis                        | CBT                       | See Newton-Howes and Wood, (175) | See Newton-Howes and Wood, (175) | Not specified; 18–65 years/ SKP                      | See Newton-Howes and Wood (175)                   | Group significant differences at 8–18 months, CBT is more effective |
| Crawford et al. (176) RCT                                | Group art therapy         | Yes/Various              | 649/activity groups plus TAU/TAU | 417 of 41+ years/17++ years/ SKP                     | Weekly sessions 90 min/12 months                  | No statistically significant difference |
| Newton-Howes and Wood (179) Meta-analysis                | CBT                       | Yes/not specified        | 602/placebo group                | Not specified SKA/18–65 years                       | 9 Studies/7–22 weeks/4, 6, 9 months                | No significant differences |
| Lynch et al. (177) Meta-analytical review of well-controlled trial | CBT                       | Yes/not specified        | 310 CBT/291 control groups      | Acute and chronic adult SKP                        | From 5 weeks to 9 months                         | CBT is no better than nonspecific controls and does not reduce relapse rates |
| Gold et al. (178) Meta-analysis RCT, CCT and pre–post study | Music therapy            | Yes/not specified        | 15 studies (n = 691 patients): 8 RCTs, 3 CCTs, 4 uncontrolled studies | Psychotic and nonpsychotic severe mental illness patients | 3–51 sessions                                    | Significant effects on general and negative symptoms, with dose effect |
| Garety et al. (179) RCT                                   | CBT, FI with and without carers | Yes/various              | 301 (1) 27 without carers TAU or CBT+TAU, (2) 106 with carers TAU, CBT + TAU or FI + TAU | Non affective psychosis/18–65 years, at least moderate severity for one symptom at PANSS | CBT and FI focusing on relapse prevention, 12–20 1-h sessions/9 months | The CBT and FI had no effects at 12 or 24 months. CBT showed effects on depression at 24 months |
| Bendall et al. (64) RCT                                   | BF                        | Yes/various              | 30 ACE/30 BF                     | Acute first episode psychosis                       | Up to 20 sessions, 45 min/14 weeks                | BF was comparable to CBT |
| Talwar et al. (180) RCT                                   | Music therapy             | Yes/not specified        | 33 music therapy + TAU/48 TAU    | Inpatients, SKA spectrum                            | 45-min weekly sessions/12 weeks                   | Significant reduction in PANSS total score |
| Bechdorff et al. (181) RCT                                | Group CBT, group PE       | Yes/not specified        | 88/40 CBT/48 PE                  | One episode of SKP or related disorder, 18–64 years | 16 sessions group CBT or 18 sessions group PE/8 weeks | Significant less re-hospitalization at 6 months RJ in CBT group |
| Tarrier et al. (166) RCT                                  | CBT, supportive counseling (SC) | Yes/TAU                  | 101 of 309 CBT + TAU/106 SC + TAU/102 TAU | SKA spectrum or delusional disorder                | An 18-month follow-up; 15–20 h plus four "booster" sessions treatment/5 weeks | Improvement at PANSS in both groups for positive and negative symptoms |
| Shahar et al. (182) Retrospective study                   | Psychoanalytically oriented treatment | No                       | 29 anaclic/34 introjective/27 mixed type | Inpatients with psychosis (50%), severe personality disorders (60%) and severe depression (10%) | Treatment including psychoanalytic psychotherapy 4 times a week/15 months | Significant improvement only in the mixed type (anaclic–introjective) at WAIS, Rorschach, and TAT |

(Continued)
| Author/type of study       | Psychological intervention | Adjunction/antipsychotic | Number of patients/control group | Stage of illnesses and/or age of patients/diagnosis                                                                 | Frequency and time sessions/duration of treatment | Results                                                                                                                                                                                                 |
|---------------------------|----------------------------|--------------------------|----------------------------------|------------------------------------------------------------------------------------------------------------------------|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Haddock et al. (183) RCT  | Individual and family-oriented CBT combined with motivational intervention for substance use problems | Yes/neuroleptics          | 18 patients and 18 carers         | Schizophrenia spectrum disorder or delusional disorder, 18-35 years and face-to-face contact with a carer for a minimum of 10 h per week. | 9 months of motivational intervention with 18-month FU period/11 around 29 sessions. R: 10-16 sessions use | There was no difference between the two groups for PANSS general or total subscale scores. SFS total scores at 18 months II had significantly superior GAF scores at the 18-month follow-up |
| Turkington et al. (184) RT | Brief CBT                  | Yes/not specified         | 257 of 422 patients              | Patients with schizophrenia in secondary care settings                                                                  | 6-h-long sessions over 2–3 months | Improvements at CPRS, IRS, BOCQ, and MRS, in overall symptomatology, carer burden, insight into CBT group                                                                                                 |
| Pilling et al. (142) Meta-analysis | Social skill training (SST), cognitive remediation (CR) | Yes/Various                | SST/CR                           | Chronic SKP/mean duration of illness: 6 ± 3 years (specified in 7 studies)                                               | 1-h session, weekly-fortnightly-monthly | No clear evidence on improvements of SST. No benefits of CR                                                                                                                                                |
| Lewis et al. (185) RCT    | CBT                        | Yes/not specified         | 101 of 309 patients              | Acute phase of first and second episode within 2 years of treatment/DSM schizophrenia spectrum                        | 15–20 h in 5 weeks plus       | PANS total and positive showed “trend” for the CBT to improve fastest; in 60% hallucination resolution in CBT > SC; TAU > SC                                                                 |
| Drury et al. (186) RCT    | CBT/recreational activities and support | Yes/Various                | 20 of 40 adjunction CBT/20       | Hospitalized patients suffering from acute episode of nonaffective psychosis                                          | 8 h for week treatment for a maximum of 6 months | PAS and PBOQ scores showed no significant variation in positive and negative symptoms                                                                                                               |
| Hogarty et al. (186) Clinical trial | Personal therapy          | Yes/minimum effective dose (not specified) | 151 randomly assigned to 1) personal therapy, 2) FI PE, 3) mixed therapy 4) ST, 54 patients randomly assigned to 1) personal therapy | SKP or SKA disorder patients after hospital discharge                                                                   | 3 years                        | Personal therapy improves the social adjustment in the 2nd and 3rd years. ST, with or without R, effective with peak at 12 months. Long-term therapy is more effective |
| Buchkremer et al. (187) RC intervention study | Psychoeducational medication management training (PMT), cognitive psychotherapy (CP), key-person counseling (KC) | Yes4.639 ± 680 (mean dose) of chlorpromazine equivalents 40% depot 49% oral 11% combined oral and depot | 132 patients/5 group: 32 PMT+ regular leisure-time group (LGT) 35 PMT + CP/34 PMT + LG T + KC/33 PMT + CP + KC/57 LGT | SKP 31.3+ years, 22.9+ at onset years, the mean number of hospitalizations: 4.7 ± 3.6, total duration of hospitalization: 56.4 ± 52.5 weeks | PMT: 10 group sessions, the first 5 at weekly interval, then at fortnightly. (6-8 persons per group) | Favorable result in PMT + CP + KC Best results in PMT + CP + KC with 24% lower rehospitalization at 1 year follow-up and 26% at 2 years follow-up |