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ORIGINAL RESEARCH

Cognitive Behavioral Therapy for Symptom Management in Treatment-Resistant Schizophrenia

This integrative review considers the evidence for CBT as an adjunct to treatment with antipsychotics.

Schizophrenia is a serious psychiatric disorder, defined by the National Institute of Mental Health (NIMH) as one "characterized by disruptions in thought processes, perceptions, emotional responsiveness, and social interactions."[1] People with the condition often struggle with psychosis, depressive symptoms, difficulty with social interactions, reduced motor function, and significant cognitive impairment. According to the NIMH, household surveys indicate that 0.25% to 0.64% of the U.S. population grapples with schizophrenia and related psychotic disorders; worldwide, the prevalence among noninstitutionalized people is estimated at 0.33% to 0.75%.[1]

While these estimates might seem small, schizophrenia is one of the leading causes of disability worldwide, and comes with high societal and economic costs.[1,2] In the United States, the NIMH estimates that on average, people with the disorder lose a staggering 28.5 years of life, primarily due to the attendant medical comorbidities, although suicide is likely a contributing factor as well.[1] Many people with schizophrenia have suicidal ideation; an estimated 25% to 50% attempt suicide[3] and nearly 5% complete suicide.[1]

Schizophrenia is notable for the numerous obstacles that patients, families, and providers may confront when pursuing treatment. One such obstacle lies with the drugs currently used to treat schizophrenia. Although the causes of schizophrenia remain unclear, it's believed that disruption in the synthesis, transmission, and regulation of the neurotransmitter dopamine plays a role in the emergence and severity of symptoms.[3] Indeed, for many patients, dopaminergic antipsychotics are effective in modulating symptom severity.[3] Yet a large subset of patients—up to 30%, according to the Treatment Advocacy Center—don't have the expected therapeutic response.[4] These individuals are recognized as having treatment-resistant schizophrenia (TRS), a form of the illness associated with substantial additional clinical and socioeconomic burdens.[5] Clinical symptoms occur with greater frequency and severity in patients with TRS than in those with non-TRS, and unemployment and hospitalization rates are also greater.

Two meta-analyses have established that clozapine outperforms other oral antipsychotics for patients with TRS.[6,7] Despite clozapine's potential side effects, including a heightened risk of severe neutropenia that requires monitoring through the Clozapine Risk Evaluation and Mitigation Strategy,[8] this agent is recognized as first-line treatment for TRS by the American Psychiatric Association (APA).[9] But many people experiencing TRS do not exhibit a full therapeutic response to clozapine alone.[5] Thus identifying additional treatment approaches is vital. Cognitive behavioral therapy

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ABSTRACT

Background: Treatment-resistant schizophrenia (TRS) comes with significant medical comorbidities, including heart disease, liver disease, and diabetes—all of which contribute to higher mortality rates and shortened life expectancy. Second-generation antipsychotic medications do not consistently alleviate psychotic symptoms, especially among patients with TRS. Clozapine, the gold standard of pharmacological treatment for TRS, offers only partial relief for many patients. Additional treatment approaches, which include cognitive behavioral therapy (CBT), are often necessary.

Purpose: The aim of this integrative review was to assess the efficacy of CBT as an adjunctive treatment for TRS in various study populations.

Methods: The Johns Hopkins Nursing Evidence-Based Practice Model and Guidelines were used to guide the review. A literature search of PubMed, CINAHL, Scopus, and PsycInfo was conducted, and a total of 66 articles were identified. Strong inclusion and exclusion criteria were applied to ensure that only high-quality studies were included for analysis.

Results: Of the eight studies that met the eligibility criteria, five indicated that CBT has statistically significant efficacy in reducing positive psychotic symptoms of TRS. There was also evidence that in implementing CBT, a follow-up period of at least six months helps to sustain improvements.

Conclusions: CBT can be a safe and effective adjunctive treatment for patients with this illness. We recommend that nurses who work in psychiatric settings, EDs, and home health or community care settings obtain training in CBT.

Keywords: antipsychotics, clozapine, cognitive behavioral therapy, treatment-resistant schizophrenia

(CBT) as an adjunctive treatment to antipsychotics has shown clinically promising results.

Purpose. This integrative review aims to answer the clinical question: "In adult patients with TRS, how does the use of oral clozapine with CBT compared to clozapine alone affect symptom severity?"

BACKGROUND AND SIGNIFICANCE

Nationally, the socioeconomic costs of TRS are enormous. It's reported that TRS adds $34 billion in direct medical costs annually to total U.S. health care costs.[10] Compared to patients with non-TRS, those with TRS have tenfold higher hospitalization costs and total health care resource usage.[10] Patients with TRS experience several comorbidities, including depression, hypertension, insomnia, and obesity, that are less common in patients with non-TRS.[5] They are also more likely to have delusions and hallucinations, to have reduced cognitive and psychosocial functioning, and to be unemployed.[5, 10]

Most second-generation antipsychotic medications have shown a concerning lack of efficacy in their ability to consistently remit the symptoms of schizophrenia in patients with TRS.[11, 12] Although it's estimated that clozapine is effective in 30% to 60% of patients who don't respond well to more commonly prescribed antipsychotics,[13, 14] up to 60% of patients with TRS who are treated with clozapine still experience psychotic symptoms that influence normal functioning.[15] Treatment adjuncts and alternatives are clearly needed. But there are few interventions available for patients with an incomplete response to clozapine.

Providers may add a second antipsychotic, but this creates further risks. The adverse effects of antipsychotics are well documented and can include extrapyramidal side effects such as drug-induced parkinsonism and tardive dyskinesia[16]; metabolic disturbances such as abdominal weight gain, diabetes, and hyperlipidemia[16]; and central cholinergic dysfunction associated with long-term cognitive impairment and dementia.[17] Adding a second antipsychotic agent may reduce medication adherence and increase the likelihood of pharmacological interactions. Alternatively, adjunctive treatment with electroconvulsive therapy (ECT) may be considered. But ECT isn't always readily accessible to patients[18] and involves an exhaustive medical clearance and informed consent process. Moreover, ECT requires the use of general anesthesia and can result in transient (or more rarely, extended) retrograde amnesia.[19]

In an article updating treatment options for TRS, Elkis and Buckley noted that CBT "has been extensively used" for treating people with schizophrenia, and that even patients with TRS have shown significant improvements in psychotic as well as general symptoms.[20] Indeed, there is evidence that CBT can be helpful in patients unresponsive to antipsychotic agents, including clozapine.[21] While both the APA's current *Practice*

Guideline for the Treatment of Patients with Schizophrenia and a recent Cochrane review acknowledge the potential benefits of CBT as an adjunctive treatment for patients with schizophrenia, both also note that the quality of the available evidence is generally low.[9,22] Concerns raised by Sensky and colleagues include small sample sizes, methodological inconsistencies, and problems with blinding.[23] Ongoing evaluation of emerging evidence on the efficacy of CBT for patients with TRS is essential to guiding best practice.

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METHODS

Framing the question. We used the Johns Hopkins Nursing Evidence-Based Practice (JHNEBP) Model and Guidelines to guide this integrative review.[24] The JHNEBP model is a powerful clinical decision-making tool that provides several user-friendly approaches for individual and group use. Our research team drafted an initial clinical research question, adopting various perspectives to understand the nuances of the research topic. Team members refined the question, defining the population, intervention, control, and outcomes (PICO) of interest to create a more specific question that could be answered by examining the relevant literature.[25] The final PICO question was "In adult patients with TRS, how does the use of oral clozapine with CBT compared to clozapine alone affect symptom severity?"

Literature search. With this research question in mind, team members conducted a search of the available research in four databases: PubMed, CINAHL, Scopus, and PsycInfo. The following search terms were used in various combinations (with British and American spellings if applicable): *clozapine*, *cognitive behavioral therapy*, *drug resistance*, *refractory*, *treatment resistance*, *schizophrenia*, and *symptom severity*, as well as the clozapine brand names *Clozaril*, *FazaClo*, *FazaClo ODT*, and *Versacloz*. The search was limited to articles published in English between January 1, 2010, and September 30, 2020. The original database search yielded 62 articles. Four additional studies were identified by manually screening the reference lists of these articles.

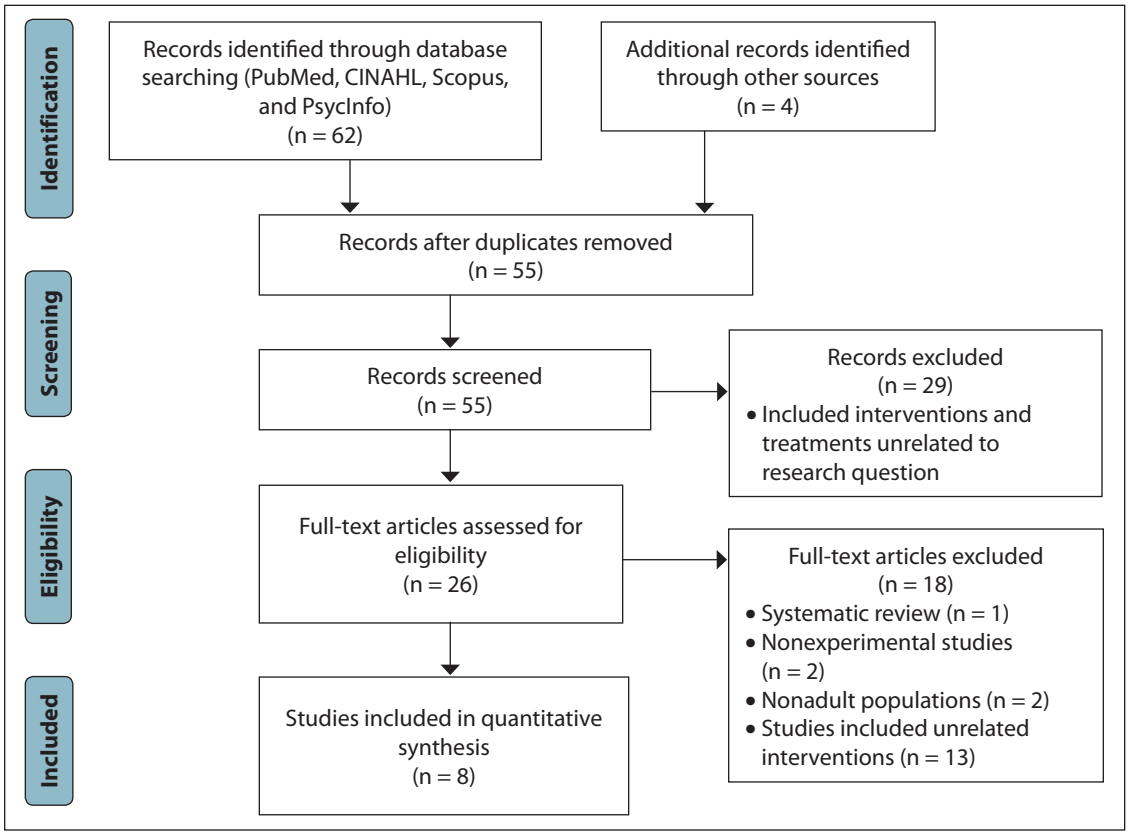
Eligibility criteria. As Charrois observed, "A systematic review is only as good as the data on which it is based,"[26] and the same is true for an integrative review. Strong inclusion and exclusion criteria were used to ensure that only studies with good internal and external validity were included. To that end, we sought to include randomized controlled trials, quasiexperimental studies, non–randomized controlled trials, meta-analyses of randomized controlled trials, as well as one randomized, single-blind, parallel-group trial. The study selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) model, which provides a 27-item list for evaluating the validity and rigor of studies.[27]

After removing duplicates, the research team identified 55 articles for possible inclusion in this review. Three reviewers—two of us (AC, DS) plus a third colleague with advanced practice training and clinical experience—read each article independently. Inconsistencies in evaluation were resolved through consensus. Twenty-nine articles were excluded because they included interventions and treatments unrelated to the research question.

To assess the eligibility of the remaining 26 articles, each title, abstract, and full-text article was independently reviewed by each team member. Eighteen articles were excluded: one was a systematic review, two were nonexperimental studies, two included nonadult populations, and 13 focused on unrelated interventions. To appraise the quality and strength of the remaining studies, the JHNEBP Evidence Level and Quality Guide (www.hopkinsmedicine.org/evidence-based-practice/_docs/appendix_c_evidence_level_quality_guide.pdf) was used. The JHNEBP Research Evidence Appraisal Tool helped guide the evaluation process,[28] and grades for each study were reached by consensus. The team members also identified commonalities across the studies to address the overarching research question. This helped to ensure that this review would draw on the most consistent findings possible. For a detailed PRISMA diagram, see Figure 1.

Synthesis. To synthesize these results, the team first used the JHNEBP Evidence Level and Quality Guide to summarize the collected information. Then we appraised the evidence using the JHNEBP Synthesis Process and Recommendations Tool.[29]

Figure 1. PRISMA Flow Diagram of Studies



PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Lastly, we discussed the consistency of the statistical findings and the potential direction of future research in this area.

RESULTS

Overall study characteristics. Eight full-text articles met the inclusion criteria, and were included in the quantitative synthesis.[11, 21, 23, 30-34] Five of the studies were randomized controlled trials,[11, 23, 31-33] two were meta-analyses of randomized controlled trials,[21, 34] and one was a non–randomized controlled trial.[30] All eight studies had Level I evidence rankings (the highest available). Regarding the quality of the evidence, four studies were graded A,[11, 23, 31, 33] three were graded B,[21, 32, 34] and one was graded C.[30]

In all the reviewed studies, participants had to be actively receiving mental health treatment and exhibiting a psychotic disorder as defined by the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) criteria. All the studies included patients with TRS and involved the use of CBT. Other inclusion criteria varied. Five of the studies required participants to have clinically significant symptoms of schizophrenia.[11, 21, 23, 30, 31] In the study by Morrison and colleagues, participants had to have one or more persistent psychotic symptoms despite receiving at least 400 mg of clozapine daily for at least 12 weeks.[11] In the study by de Paiva Barretto and colleagues, participants were required to have persistent symptoms after at least six months of clozapine treatment.[30] A symptom severity rating of 4 or greater on the Brief Psychiatric Rating Scale–Anchored (BPRS-A) was also required. In all eight studies, patients were receiving antipsychotic medications: five studies named clozapine specifically[11, 21, 30, 32, 33]; two studies cited the use of atypical antipsychotics without naming clozapine,[23, 31] and one simply noted the use of "appropriate" medications.[34] In all eight studies, antipsychotic medications were stopped if adverse reactions developed.

Seven of the eight studies incorporated individual counseling in various ways.[11, 21, 23, 30-33] For example, in the study by de Paiva Barretto and colleagues, all participants attended weekly individual therapy sessions: the intervention group received CBT and the control group received "befriending," a form of nonspecific psychosocial support.[30] In the study by

Pinto and colleagues, participants in the experimental group received CBT and social skills training, while those in the comparison group received "supportive" psychotherapy.[32]

tial as an effective adjunctive treatment for the positive symptoms of psychosis. (Positive symptoms are abnormal and present, such as hallucinations or delusions; negative symptoms are abnor-

CBT shows potential as an effective adjunctive treatment for the positive symptoms of psychosis.

The meta-analysis by Burns and colleagues evaluated 12 randomized controlled trials published between 1993 and 2010.[21] For inclusion, all participants had to be receiving psychiatric treatment for psychosis and to exhibit symptoms despite at least three months' treatment with antipsychotics. A majority had a diagnosis of schizophrenia, schizoaffective disorder, or delusional disorder. Patients in the experimental groups received CBT as an adjunctive treatment; those in the control groups received treatment as usual or another adjunctive psychosocial treatment or were on waiting lists. In three of the eight studies reviewed here, patients received CBT in addition to standard antipsychotic treatment.[11, 31, 34] The meta-analysis by Wykes and colleagues evaluated 34 studies published between 1978 and 2006. For inclusion, all participants had to be receiving psychiatric treatment, and a majority of participants in each study had to have a diagnosis of schizophrenia. Participants in the experimental groups received CBT for psychosis (CBTp) plus treatment as usual; those in the control groups received treatment as usual.

The reviewed research took place in various nations, including Brazil,[30] Italy,[32] The Netherlands and Belgium,[33] the United Kingdom (UK),[11, 23] and the United States.[31] The two meta-analyses were also multinational.[21, 34] Of the eight studies, three randomized controlled trials were multisite. One UK study was conducted among patients at five community-based and inpatient mental health services sites.[11] Another UK study recruited patients from five clinical services sites.[23] The third study was conducted in various mental health hospitals throughout The Netherlands and in one hospital in Belgium.[33] That last study was the only one conducted solely in inpatient settings.[33]

For more details on the eight reviewed studies, see Table 1.[11, 21, 23, 30-34]

DISCUSSION

CBT as adjunctive treatment. Overall, all eight studies demonstrated that CBT shows potenmal absences, such as a lack of motivation (avolition) and a lack of interest (anhedonia). Five studies found that participants in the CBT intervention groups experienced superior outcomes compared with participants who received befriending[23, 30] or treatment as usual.[31, 33, 34]

CBT vs. treatment as usual. Valmaggia and colleagues conducted a study among 50 inpatients with TRS who were treated with antipsychotic agents; a majority were receiving clozapine or another atypical agent.[33] During the study, all medication regimens remained stable. Participants were randomized to receive either adjunctive CBT or supportive counseling (29 and 21 participants, respectively), but only 42 participants completed the follow-up analysis. The researchers found that CBT was more effective at alleviating auditory hallucinations, although not delusions; the relatively small sample size was a limitation.

In a larger trial, Morrison and colleagues conducted a nine-month study among 425 patients with clozapine-resistant TRS.[11] Participants received either CBT plus treatment as usual or treatment as usual alone. Although the CBT group experienced modest improvements at nine months, no statistically significant difference in total scores on the Positive and Negative Syndrome Scale (PANSS) were found at 21 months' follow-up. The researchers noted several limitations: in the CBT group, the 26 hours of engagement between therapists and participants may have been insufficient, and in the treatment-as-usual group, the frequency of contact between research assistants and participants was not controlled. Although Morrison and colleagues stopped short of recommending CBT, they suggested it be offered "as a pragmatic individual trial," possibly for an extended intervention period.[11]

Grant and colleagues conducted an 18-month study among 51 patients with schizophrenia for whom treatment with antipsychotics had had "limited efficacy."[31] Participants received either CBT plus standard treatment or standard treatment

alone. The patients who received CBT showed significant improvements in positive symptoms and overall functionality. Like Morrison and colleagues, Grant and colleagues noted that patients assigned to CBT had more contact with therapists than those receiving standard treatment and suggested further research to investigate "nonspecific patient contact factors."

CBT vs. befriending. In the study by de Paiva Barretto and colleagues, participants in both the befriending and CBT groups had decreasing scores on the PANSS positive subscale over the 21-week study period, although the difference was only significant in the CBT group.[30] This finding was indicative of improved general psychopathology. But at six months' follow-up, only the CBT group participants continued to show reduced psychotic symptoms. Similarly, in the study by Sensky and colleagues, both the befriending and CBT group participants showed significant short-term improvements.[23] Yet at nine months' follow-up, only the CBT group showed sustained benefits. Sensky and colleagues suggest that patients with schizophrenia can benefit from regular therapeutic sessions "with someone attentive to their interests and . . . willing to interact with them socially," and note that CBT offers the added advantage of teaching patients a range of skills for managing symptoms more effectively.

Considered together, the research suggests that in implementing CBT, a follow-up period of at least six months is beneficial to ensure lasting clinical improvements.

the cumbersome eligibility and clearance processes associated with ECT,[18] CBT offers an important option for patients and providers seeking to add a low-risk, more readily accessible intervention in the treatment of TRS.[16, 35]

In working with patients who have TRS, nurses can implement a variety of CBT techniques to alter negative thought processes and maladaptive beliefs. It can be useful to first identify cognitive distortions, such as mind reading (believing one knows what another person is thinking) and personalization (believing one is the cause of another's negative actions, without considering other plausible explanations).[36] Then, rather than directly challenging the patient's delusions, the nurse can guide the patient in examining the consequences—which often include fear, isolation, or interpersonal conflict—and encourage them to generate more adaptive explanations. For example, the patient might interpret a stranger's frown in the grocery checkout line as an intent to harm her. An alternative explanation might be that the checkout line is long, and the stranger is already late for an appointment.

Along with developing reality-testing skills, practicing this technique can help patients to achieve greater insight into their condition.[36] It's important to note that CBT can be used to normalize schizophrenia because successful treatment doesn't depend on eliminating hallucinations and delusions; rather, it fosters the ability to live a fulfilling, independent, and productive life.[35] Moreover, behavioral activation, a key component of CBT, can help combat refractory negative symptoms of TRS such as anhedonia, avolition, and asociality.[3, 35] By acquiring targeted CBT skills, patients with TRS can become more active participants in their lives, and in so doing can increase their sense of belonging and their capacity for meaningful experiences and relationships.

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Implications for practice. In light of our findings, we recommend that CBT be incorporated as an adjunctive treatment to clozapine for patients with TRS, although several qualifications must be stated. As noted above, Morrison and colleagues found that at 21 months, CBT plus treatment as usual wasn't superior to treatment as usual alone.[11] Moreover, in the meta-analysis by Wykes and colleagues, CBTp had an unremarkable effect size for negative symptoms,[34] which are generally less responsive to treatment than positive symptoms.[3] That said, given the well-known adverse effects associated with adjunctive psychotropic agents and

We encourage nurses who work with psychiatric populations to seek continuing education in CBT; nurses in many other care settings (including EDs, home health care, and community care clinics) can benefit from using CBT skills, when relevant, in patient encounters. Our findings also

Table 1. Summary of Reviewed Studies

Study	Evidence Type and Study Design	Characteristics of Sample and Setting	Results	Evidence Level and Quality Grade[a]
Burns AMN, et al. 2014[21]	Meta-analysis of 16 articles covering 12 randomized controlled trials	552 subjects with schizophrenia, schizoaffective disorder, or delusional disorder, and exhibiting positive symptoms despite treatment with antipsychotics, were assigned to receive either CBT (experimental groups) or treatment as usual or another psychosocial treatment or were wait-listed (control groups). Studies were published between 1993 and 2010.	Overall, CBT demonstrated beneficial posttreatment effects on both positive and general symptoms of psychosis, and these effects were sustained at 3 to 18 months' follow-up. The authors concluded that CBT shows strong potential as an effective adjunctive treatment for patients with medication-resistant positive symptoms of psychosis.	Level I Grade B
de Paiva Barretto EM, et al. 2009[30]	Experimental non–randomized controlled clinical trial	21 outpatient subjects with TRS and BPRS-A severity ratings of 4 or greater were allocated to receive either CBT (n = 12) or befriending (n = 9) for 21 weeks. Study was conducted at the Schizophrenia Program of the Institute of Psychiatry at the University of São Paulo Medical School, São Paulo, Brazil.	Compared with controls, the CBT group had significantly reduced scores on the BPRS-A and both the PANSS general psychopathology and positive subscales. The CBT group also showed a significant difference over time with regard to total PANSS scores. The difference was sustained at 6 months' follow-up.	Level I Grade C
Grant PM, et al. 2012[31]	Experimental randomized single-blind parallel group trial	51 subjects diagnosed with schizophrenia and impaired neurocognition were randomly assigned to receive either CBT plus standard treatment (n = 27) or standard treatment alone (n = 24) for 18 months. Study was conducted at a single U.S. treatment center between January 2007 and August 2009.	Compared with subjects receiving only standard treatment, subjects who also received CBT showed substantial reductions in positive symptoms and improvements in daily functioning. Those in the CBT group had a greater decrease in avolition–apathy per the SANS global subscale as well. Group differences were "statistically significant and clinically meaningful."	Level I Grade A
Morrison AP, et al. 2018[11]	Experimental randomized controlled trial	425 subjects diagnosed with schizophrenia, schizoaffective disorder, or delusional disorder and exhibiting positive symptoms despite treatment with clozapine were randomized to receive either CBT plus treatment as usual (n = 209) or treatment as usual alone (n = 216) for 9 months, with a 21-month follow-up. Study was conducted from January 2013 through May 2015 in 5 community-based and inpatient mental health service sites in the United Kingdom.	Compared with control groups, the CBT groups had small but significant improvements on PANSS total scores at 9 months. At 21 months, no difference between groups was evident. A small percentage of subjects in both groups (13% of CBT groups, 7% of controls) showed more than 50% improvement in PANSS total scores at 21 months.	Level 1 Grade A

Pinto A, et al. 1999[32]	Experimental randomized controlled clinical trial	37 inpatient and outpatient subjects with TRS who were being treated with clozapine were randomized to receive either CBT plus social skills training (n = 19) or supportive therapy alone (n = 18) for 6 months. Study was conducted from October 1996 to February 1998 through the treatment research unit of the Department of Mental Health of the Province of Naples in Pollena, Italy.	Both groups showed statistically significant improvements on the BPRS, SAPS, and SANS from baseline to 6 months' posttreatment. Those in the CBT group had lower BPRS and SAPS scores than those in the control group.	Level I Grade B
Sensky T, et al. 2000[23]	Experimental randomized controlled trial	90 subjects with TRS were randomized to receive either CBT (n = 46) or befriending (n = 44). Study was conducted at 5 clinical services in the United Kingdom (2 in West London and 3 in northern England) over a 9-month period, with additional 9-month follow-up.	Both groups showed significant benefits at 9 months. Only the CBT group demonstrated lasting gains at 9 months' follow-up on all 4 outcome measures (CPRS total, CPRS schizophrenia change, MADRS, SANS scores). Significantly more subjects in the CBT group had 50% or greater reductions in CPRS total and CPRS schizophrenia change scores at 9 months' follow-up, compared with those in the befriending group.	Level I Grade A
Valmaggia LR, et al. 2005[33]	Experimental randomized controlled clinical trial	50 inpatient subjects with TRS were assigned to receive either CBT (n = 29) or supportive counseling (n = 21) for 22 weeks, with a 6-month follow-up. Study was conducted at an unspecified number of mental hospitals in The Netherlands and in one in Belgium. Recruitment lasted 3 years.	At initial posttreatment assessment, a larger percentage of subjects in the CBT group than the control group showed at least a 20% reduction on the PANSS positive subscale. More specifically, subjects in the CBT group demonstrated greater improvement with regard to auditory hallucinations and illness insight. But this between-group difference wasn't sustained at the 6-month follow-up.	Level I Grade A
Wykes T, et al. 2008[34]	Meta-analysis of 34 articles covering 34 randomized controlled trials	Most subjects had a diagnosis of schizophrenia and were actively receiving psychiatric services. Subjects were randomized to receive either CBTp plus treatment as usual or only treatment as usual. Studies were published between 1978 and 2006.	CBTp demonstrated a modest significant effect size for positive symptoms of psychosis. CBTp also appeared to have some impact on negative symptoms, functioning, and mood, although these effect sizes lacked significance.	Level I Grade B

BPRS = Brief Psychiatric Rating Scale; BPRS-A = Brief Psychiatric Rating Scale–Anchored; CBT = cognitive behavioral therapy; CBTp = Cognitive Behavioral Therapy for Psychosis; CPRS = Comprehensive Psychiatric Rating Scale; MADRS = Montgomery–Asburg Depression Rating Scale; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; TRS = treatment-resistant schizophrenia.

[a]Per the Johns Hopkins Evidence Level and Quality Guide (www.hopkinsmedicine.org/evidence-based-practice/_docs/appendix_c_evidence_level_quality_guide.pdf).

underscore the need for interprofessional collaboration. For example, we encourage nurses in various settings who encounter patients with TRS to maintain a referral list of therapists specializing in CBT or CBTp.

Limitations. Four of the eight reviewed articles had small sample sizes of 30 or less in each study arm,[30-33] which limits the power of the findings. Moreover, the two meta-analyses each included articles that are also included in this review: three[23, 32, 33] in the meta-analysis by Wykes and colleagues,[34] four[23, 30, 32, 33] in the meta-analysis by Burns and colleagues.[21] This rather high degree of twice-evaluated data might have resulted in overemphasis of the evidence demonstrating CBT's efficacy in reducing psychotic symptoms. Another limitation is the paucity of available articles addressing the topic of this review. If a larger body of research had existed, our team might have obtained a more definitive answer to the research question. Lastly, it's worth noting that all but one of the reviewed studies were conducted more than five years ago. This too may affect the quality of the evidence synthesis and diminish the strength of our recommendations.

CONCLUSIONS

The findings of this integrative review suggest that CBT can benefit patients struggling with the considerable challenges of TRS. CBT is most effective when used in conjunction with an antipsychotic medication. It can be readily incorporated into a patient's plan of care. Moreover, CBT will not increase the risk of extrapyramidal side effects (as would adding another first-generation antipsychotic) or the risk of cardiometabolic conditions (as would adding a second-generation antipsychotic).[3]

This review reveals the limitations of the existing literature—in particular, the scarcity of more recent randomized controlled trials with large sample sizes—and underscores the need for further research. A common limitation in the reviewed studies concerned variables such as the frequency and duration of therapist–participant contact.[11, 31] Controlling for inconsistencies in such variables would help in determining what amount of CBT confers the greatest benefit to patients with TRS. As the treatment goal for schizophrenia shifts away from reducing positive symptoms and toward improving global functioning,[35] future studies should use subjects' level of functionality as a primary outcome. Our findings also have important practice implications. Nursing professionals from bedside nurses to NPs, whether working in acute or in community settings, can advocate the use of CBT as a vital tool for treating people with TRS.

Lastly, we wonder whether the dearth of recent research on this topic might be indicative of a decline in the clinical use of CBT, a reduced emphasis on CBT in training programs, or the constraints of today's fast-paced, pharmacologic-centric model of psychiatric care. These are important questions in our ongoing efforts to improve the lives of patients with TRS. ▼

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