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Evidence-Based Review of Pharmacologic and Nonpharmacologic Treatments for Older Adults with Schizophrenia

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Longitudinal studies of the course of schizophrenia show that a majority of individuals affected by this disorder experience clinically significant reduction and even remission of symptoms with aging [1], yet many individuals with schizophrenia continue to experience debilitating symptoms in older age. Furthermore, approximately 20% of middle-aged and older persons who have schizophrenia experience the first onset of their symptoms after the age of 45 [2]. Schizophrenia has a negative impact on the functioning and well-being of many older affected adults [1,3] and is associated with heightened morbidity, health care use, and costs and even increased mortality [4–6]. Demographic projections indicate that the aging of the ''baby boom'' generation will increase the proportion of Americans over age 65 from 13% currently to 20% by the year 2030 [7]. This percentage represents an expected increase in the number of people over age 65, from 35 million to 71 million people [7]. Moreover, the number of older people who have psychiatric disorders including schizophrenia will likely increase disproportionately compared with older people in the general population, in part because improved treatments may lower mortality rates in younger adults who have

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serious mental illnesses, allowing more of them to live to old age [8]. Approximately 140,000 persons or 0.4% of older Americans have a diagnosis of schizophrenia [9]. If population projections are accurate, within 25 years this figure will more than double to nearly 300,000.

Several evidence-based reviews have been published evaluating the effectiveness of treatments for schizophrenia, that focus on younger adults [10–14], and over 56 topic reviews exist in the Cochrane Database of Systematic Reviews. Only one Cochrane Database review evaluates the treatment of older adults who had schizophrenia [15]. This 1990 review is limited to the evaluation of a randomized clinical trial (RCT) of remoxipride [16], an agent that was pulled from the market because of safety concerns. Evidence-based reviews of treatment for younger adults who had schizophrenia, combined with general reviews of treatment for older adults who had schizophrenia [17–19], indicate that antipsychotic drugs coupled with psychosocial interventions should be the mainstay of treatment for persons who have schizophrenia.

Despite an extensive literature on effective interventions for younger adults who have schizophrenia, the results of these studies do not necessarily translate to older adults because of age-associated changes in physiologic, social, and cognitive functioning. Changes in cognition, metabolism, receptor sensitivity, and psychologic development can alter the effects of both psychotherapeutic interventions and pharmacologic responses. The additional burden of medical comorbidity and potential drug–drug interactions associated with polypharmacy further complicate treatment. Older people experience increased sensitivity and a greater likelihood of medication side effects [20]. For example, compared with their younger counterparts, older adults who have schizophrenia experience more severe extrapyramidal symptoms (EPS) and higher rates of tardive dyskinesia [21]. Antipsychotic medications may also differentially cause problems such as cognitive impairment and cardiovascular effects in older people. Generally, physicians may attempt to adjust for these risk factors by prescribing lower daily doses of antipsychotic and anticholinergic medications [1]. The selection of appropriate and optimal treatments for older patients who have schizophrenia should accommodate age-associated pharmacokinetic and pharmacodynamic changes and reflect a critical ascertainment of the evidence supporting alternative treatment options.

This review evaluates the evidence for the provision of pharmacologic and nonpharmacologic treatments for older persons who have schizophrenia. Specifically, this review addresses whether treatments for older adults who have schizophrenia are effective in improving symptoms and are well tolerated.

Data sources and search strategy

To identify relevant articles for this review, two strategies were followed. A review of pharmacologic studies was conducted using the following

strategy. PubMed, PsychINFO, CINAHL, and BIOSIS were searched within three topic areas for English language articles indexed through May 2005: pharmacologic treatment (keywords: antipsychotic, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone), schizophrenia, and older adults (keywords "geri," late-life, senile, elder, "gero," and older in the title). Additional articles were identified through a bibliographic review and through PubMed and Web-of-Science "related records" searches. The review of nonpharmacologic intervention studies was conducted through the following strategy. PubMed and PsychINFO were searched within three topic areas for English language articles indexed through May 2005: psychosocial treatment (keywords psychosocial, skills training, and cognitive behavioral), schizophrenia, and older adults (keywords elder, geri, older, and older adults). Additional articles were identified through a bibliographic review.

Criteria for selected studies

Studies were included if they evaluated the efficacy and safety of pharmacologic and nonpharmacologic interventions in older adults who had schizophrenia or schizoaffective disorder. Pharmacologic trials included those that focused entirely on older adults (age ≥ 50) who had schizophrenia or schizoaffective disorder. This review excluded literature examining heterogeneous samples and the limited literature on treatment for paraphrenia. Nonpharmacologic interventions included studies with samples in which 50% or more of participants were diagnosed with schizophrenia or schizoaffective disorder or studies in which outcomes were separately reported for these disorders in middle-aged or older persons (age ≥ 40). The distinction in diagnostic inclusion criteria was developed because of the nature of interventions that focus on functional impairment, as opposed to biological mechanisms. The distinction in age criteria reflects the availability of interventions targeting older persons who had schizophrenia.

Eligible pharmacologic studies consisted of RCTs, quasi-experimental studies, or longitudinal outcome studies consisting of 100 or more patients. Fourteen pharmacologic studies fulfilled all inclusion criteria. Eligible nonpharmacologic studies consisted of two RCTs, two quasi-experimental studies, and one uncontrolled prospective cohort study. To our knowledge, this represents all of the studies of psychosocial interventions for older adults that have been published to date, in which samples included at least some percentage of individuals who had schizophrenia.

Data extraction and analysis

Descriptive characteristics, outcome, and tolerability data were abstracted from all of the studies selected for this review. The data included study type, agent and dose or model descriptions, sample characteristics, duration and completeness of follow-up, study measures and outcomes, and strengths

and weaknesses. Primary outcomes of interest included improvement in psychiatric symptoms, functioning, and tolerability. The statistical aggregation of data was not feasible because of the lack of similarity among studies with respect to study design, intervention characteristics, inclusion criteria, and outcome measures.

Pharmacologic studies

Identification of studies

Among the fourteen pharmacologic studies that met inclusion criteria, five studies were double-blind RCTs [22–27], two studies reported the results of open-label RCTs [28,29], two studies were quasi-experimental studies [30,31], and two studies reported on noncontrolled prospective cohort studies [32,33]. In addition, two randomized controlled augmentation studies were identified, including one double [34] and one single blind [35] trial. Finally, one additional RCT was identified [16]; however, it was not included in this review because it examined the effectiveness of an agent (remoxipride) that has been removed from the market [36].

Antipsychotic agents

As shown in Table 1, five unique double-blind RCTs evaluated the effectiveness of antipsychotic agents for older adults who had schizophrenia. Two studies examined the effectiveness and safety of conventional antipsychotic agents [22,23]; two studies compared the results of atypical antipsychotic agents with conventional antipsychotic agents [24,25]; and one recent trial compared the effectiveness of olanzapine with risperidone [26,27]. Results from all of these studies generally showed improvement in psychiatric symptoms. Studies comparing atypical and conventional antipsychotics have suggested that olanzapine has superior efficacy and less severe EPS compared with haloperidol [25] and that clozapine and chlorpromazine are equally efficacious [24]. However, the available studies evaluating clozapine and conventional antipsychotics had small sample sizes [22–25] and were restricted to inpatients [22,24] and largely male Veterans Affairs populations [23,24]. These limitations warranted caution in the interpretation and generalizability of these studies. A head-to-head comparison of two atypical antipsychotic agents (olanzapine and risperidone) suggests that these agents have similar effects on cognitive [27] and psychiatric symptoms [26]. There were no significant differences in side effects between these two drugs, except for greater weight gain with olanzapine [26]. Of note, only one study included a placebo group; however, this study evaluated relapse and hospitalization after the discontinuation of antipsychotic treatment and did not evaluate the side effects or effectiveness of pharmacologic treatment for reducing psychopathology or improving functioning [23].

Table 1
Double-blind randomized controlled trials of antipsychotic medications in older adults with schizophrenia

Study	Study design	Agent	Sample	Follow-up	Outcome measures and results	Limitations and comments
Branchey et al 1978 [22]	Double-blind crossover design FLU/THIO: n = 30	FLU mean dose at endpoint 285 mg/wk THIO mean dose at endpoint 5 mg/wk	Hospitalized pts; age, 67; Female, 53.3%; Dx, chronic schizophrenia	4-wk washout period; first 8-wk active phase (half received THIO, half received FLU); 4-week washout period; second 8-wk active phase (half received FLU, half received THIO)	CGI improved in both groups: no difference between groups; BPRS anergia and total improved in both groups; BPRS emotional withdrawal improved in THIO; THIO better than FLU in reducing tension but had more severe motor retardation; rigidity and tremor increased with both drugs; FLU had more rigidity than THIO; THIO had decreased blood pressure and weight gain	Small sample size; no mention of dropout rate

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Table 1 (*continued*)

Study	Study design	Agent	Sample	Follow-up	Outcome measures and results	Limitations and comments
Ruskin and Nyman, 1991 [23]	Double-blind RCT; HAL: n = 11 PBO: n = 12	All stabilized on HAL, then randomized to HAL or PBO HAL: mean dose not stated PBO stabilized dose of HAL cut in half for 2 wk and then terminated	VA outpatients; age, 60.1; female, 0%; Dx, schizophrenia, receiving neuroleptics	6 mo; Discontinued: HAL, 27.3%; PBO, 16.6% (35 people entered trial; prior to randomization, 2 decided to drop out, 10 could not tolerate HAL)	Relapse: HAL, 12.5%; PBO, 50% Hospitalized: HAL, 0%; PBO, 10% Relapse was predicted by age, dose of neuroleptic prior to study entry, placebo, BPRS psychosis score, and years since last hospitalization	Small sample size; symptom outcomes not reported; side effects not reported
Howanitz et al 1999 [24]	Double-blind RCT; CLOZ: 24 CHLOR: 18	Flexible dose schedule: CLOZ began at 12.5 mg/d, increased to 300 mg/d; mean dose 300 mg/d CHLOR began at 25 mg/d, increased to 600 mg/d; mean dose 600 mg/d	VA inpatients CLOZ: age, 65; female, 8.3% CHLOR: age, 68.5; female, 5.6%; Dx, chronic schizophrenia/ schizoaffective and PANSS $\geq$ 60	Efficacy assessed after 12 wk Discontinued: CLOZ, 12.5%; CHLOR, 38.9%	PANSS total, positive, negative, and global scores and CGI improved in both groups; no between-group differences	Small sample size; 16/42 patients had hematologic abnormalities; percentage of adverse events equal in both groups; benztropine and chloral hydrate administered when needed for side effects and agitation

Kennedy et al 2003 [25]	Double-blind RCT OLZ: n = 83 HAL: n = 34	OLZ mean modal dose 11.9 mg/d HAL mean modal dose 9.4 mg/d	Age, 66.0 (±4.6); female, 61.5%; Dx, schizophrenia	6-week; Discontinuation: because of adverse event: OLZ: 1%; HAL, 3%; lack of efficacy, OLZ, 22%; HAL, 44%; those with ≥40% BPRS reduction continued for 52 weeks	OLZ greater improvement than HAL on BPRS total and negative factor, and PPCT, psychosis core total, delusions item, ANX/DEP, and NEG factor; clinical response (≥40% decrease in BPRS score) achieved by 51% of OLZ and 29% of HAL (p = .08); no change in CGI, MADRS, SF-36, QLS, PANSS hallucinations, agitation, positive, or cognitive factor; less EPS for OLZ vs HAL with treatment by age effect	Post-hoc analysis; small sample size; safety: OLZ superior to HAL for SAS and BAS
Jeste et al 2003 [26]	Double-blind RCT; OLZ: n = 88 RIS: n = 87	OLZ mean modal dose 11.1 mg/d RIS mean modal dose 1.9 mg/d	OLZ: age, 71.4 (± 5.6); female, 68.2% RIS: age, 70.9 (± 5.6); female, 60.9%; Dx, schizophrenia/ schizoaffective and PANSS 50–120	8 wk; Discontinued: OLZ, 19.3%; RIS, 27.6%	Ham-D, CGI, and PANSS total and POS, NEG, DIS, and ANX/DEP subscales improved in both groups; clinical improvement ≥ 20% reduction in PANSS total, OLZ, 59%; RIS, 58%; also, 32.5% of RIS and 36.0% of OLZ rated as much or very much improved at endpoint; no difference between OLZ and RIS	Adverse events: RIS, 9.2%; OLZ, 15.9%; weight gain in both groups but less frequent in RIS; no change in PANSS hostility/ excitement scale

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Table 1 (*continued*)

Study	Study design	Agent	Sample	Follow-up	Outcome measures and results	Limitations and comments
Harvey et al 2003 [27] (same study and sample as Jeste et al 2003 [26])	Double-blind RCT; OLZ: n = 89 RIS: n = 87	OLZ mean dose 11.5 mg/d RIS mean dose 2 mg/d	OLZ: age, 71.4 (± 5.9); female, 66% RIS: age, 71.2 (± 6.0); female, 62%; Dx, schizophrenia/ schizoaffective and PANSS 50–120	8 wk; 87.4% completed ≥ 1 post-baseline cognitive tests (OLZ = 79; RIS = 74); Discontinued: OLZ, 30.4%; RIS, 27.0%	Attention and memory improved in both groups (TMT-A and SVLT); substantial improvement on TMT-A seen for 25% of OLZ and 18% of RIS; executive function and verbal fluency improved in RIS but not OLZ (TMT-B, WCST total error score, VFE sum of categories and letters); no differences between OLZ and RIS	Side effects of treatment and symptom outcomes reported in Jeste et al 2003 [26]; no change in CPT total scores or WCST categories score

Abbreviations: ANX/DEP, anxiety and depression; BAS, Barnes Akathisia Scale; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression Scale; CHLOR, chlorpromazine; CLOZ, clozapine; CMAI, Cohen-Mansfield Agitation Inventory; CPT, Continuous Performance Test (measure of attention); DIS, disorganized thoughts; Dx, diagnosis; EPS, extrapyramidal symptoms; FLU, fluphenazine; HAL, haloperidol; Ham-D, Hamilton Depression Scale; MADRS, Montgomery-Asberg Depression Rating Scale; NEG, negative; OLZ, olanzapine; PANSS, Positive and Negative Syndrome Scale; PBO, placebo; POS, positive; PPCT, PANSS Psychosis Core Total; QLS, Heinrichs-Carpenter Quality of Life Scale; QOL, World Health Organization Quality of Life questionnaire; RIS, risperidone; SAS, Simpson-Angus Scale; SF-36, medical outcomes study 36-item short form; SVLT, Serial Verbal Learning Test (measure of memory); THIO, thioridazine; TMT-A, Trail Making Test, part A, visuomotor speed (measure of attention); TMT-B, Trail Making Test, part B, visuomotor speed and the ability to alternate between sets (measure of executive function); TYP, typical or conventional antipsychotics; VA, Veterans Affairs; VFE, verbal fluency examination; WCST, Wisconsin Card Sorting Test (measure of executive function).

Open-label RCTs [28,29], quasi-experimental studies [30,31], and large prospective single-agent trials [32,33] of antipsychotic treatment for older adults who had schizophrenia are shown in Table 2. These studies help to further establish the evidence base for antipsychotic treatment in this population. The open-label RCTs have indicated that olanzapine and risperidone were associated with less parkinsonism and a greater improvement in negative and depressive symptoms after crossover from conventional antipsychotics [29], and olanzapine was associated with a greater improvement than haloperidol in reducing Positive and Negative Syndrome Scale (PANSS [37]) total scores, negative symptoms, and the clinical global severity of disease [28]. A prospective quasi-experimental study found no difference in symptom improvement between a large sample receiving olanzapine and a smaller sample receiving either risperidone or a conventional antipsychotic [31]. A retrospective quasi-experimental study has indicated that risperidone had fewer side effects and was more effective in improving PANSS total scores, positive symptoms, and clinical global severity, compared with conventional antipsychotics [30]. In addition, two large prospective single-agent studies of risperidone have indicated that it was associated with improved positive and negative symptoms as well as improved clinical global impression [32,33]. This set of studies should be interpreted with caution because of a variety of study characteristics, including the lack of blinded evaluation [28–33], small sample sizes [28–30], a lack of randomization [30,31], the retrospective nature of the evaluation [30], and the absence of a comparison group [32,33].

In addition to the literature reviewed above, several small single-agent open-label studies have evaluated the use of aripiprazole [38], clozapine [39,40], fenfluramine [41], haloperidol [42], olanzapine [43,44], quetiapine [45,46], risperidone [47–49], and thiothixene [50] in older adults who have schizophrenia. Moreover, several studies have examined clozapine [51–56], haloperidol [57], olanzapine [58–60], quetiapine [61–63], risperidone [59,60,64–66], and thioridazine [57] in heterogeneous samples that included older adults who had schizophrenia.

Dosing of antipsychotic agents

Generally, the dosing of antipsychotic agents in the studies that met inclusion criteria for this review began at low levels and then increased to a targeted level. Mean olanzapine dosages were similar across studies (9.9–13.1 mg/d) [25–29,31]. Mean risperidone dosages were similar in the three RCTs (1.7–2.0 mg/d) [26,27,29] but were higher in nonrandomized studies (2.3–4.2 mg/d) [31–33,67]. Among the studies evaluating the effectiveness of haloperidol, mean dosages ranged from 7.2 to 9.4 mg/d [25,28]. Finally, mean antipsychotic dosages for those agents that were evaluated in only one of the reviewed studies included clozapine at 300 mg/d [24], chlorpromazine at 600 mg/d [24], fluphenazine at 285 mg/d [22], and thioridazine at 5 mg/d [22].

Table 2
Open-label RCTs, quasi-experimental studies, and large prospective Studies (n $\geq$ 100) of antipsychotic medications in older adults with schizophrenia

Study	Study design	Agent	Sample	Follow-up	Outcome measures and results	Limitations and comments
Open-label RCT						
Barak et al 2002 [28]	Open-label RCT; OLZ: n = 10 HAL: n = 10	OLZ, mean dose 13.1 mg/d (range 5.0–25.0 mg/d); HAL mean dose 7.2 mg/d	Age 69.2 ($\pm$6.1); female 50%; Dx, schizophrenia and PANSS $\geq$ 50	$\geq$3 mo; mean duration 15 $\pm$ 8 mo; Discontinued: OLZ, 40% (3 no response, 1 administrative); HAL, 40% (1 no response, 3 EPS)	OLZ, decrease in PANSS total and negative scores; HAL, no change in PANSS subscales or CGI; OLZ superior to HAL in reducing PANSS total and negative scores and CGI; No between-group differences on PANSS positive and general subscales	Small sample sizes; evaluators not blind to treatment; OLZ had fewer EPS than HAL; mean weight increase in both groups

Ritchie et al 2003 [29]	Open-label RCT; crossover from TYP; OLZ: n = 34 RIS: n = 32	Started switch at 5 mg/d OLZ or 0.5 mg/d RIS; after switch, OLZ mean dose 9.9 mg/d; RIS mean dose 1.7 mg/d	Age 69.6 (± 6.2); female 71.2%; Dx, schizophrenia	Switch completed after 4 weeks, plus 2 consecutive visits on same dose and no TYP; mean length to crossover: OLZ, 40.6 d; RIS, 40.4 d; Early treatment failures (death, side effects, non-compliance, marked deterioration, protocol violation) OLZ, 11.8%, RIS, 31.2%	BPRS, SANS, and MADRS scores improved during crossover in both groups; no between-group differences; OLZ, improved QOL on psychologic, physical well-being, and perceived health status; RIS, no effect on QOL; OLZ better than RIS on psychologic domain on QOL; switching from TYP to RIS or OLZ both associated with improved parkinsonism, and OLZ alone associated with reduced dyskinetic symptoms	Small sample sizes; evaluators not blind to treatment; both had improved parkinsonism; OLZ had reduction in dyskinetic symptoms

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Table 2 (*continued*)

Study	Study design	Agent	Sample	Follow-up	Outcome measures and results	Limitations and comments
Quasi-experimental studies						
Barak, et al 2002 [30]	Retrospective quasi-experimental; RIS: n = 26; TYP: n = 25	RIS mean dose 2.3 mg/d; TYP mean dose 280.7 mg/d chlorpromazine equivalents (36% of TYP sample received HAL)	Inpatients; age 72.7 (5.9); female 59%; Dx, schizophrenia/ schizoaffective and PANSS $\geq$ 55	6 and 18 months; Discontinuation: RIS, 19% (n = 1 EPS, n = 2 lack of efficacy, n = 2 treatment no longer needed); TYP, 12% (n = 3, severe EPS)	CGI and PANSS total improved in both groups at 6 and 18 mo; RIS, PANSS POS, NEG, GEN subscales improved at 6 and 18 mo; TYP, PANSS POS subscale improved at 6 and 18 mo; RIS improved more than TYP in PANSS positive and total score and CGI; clinical improvement (CGI $\leq$ 3) for 58% RIS and 29% TYP; no differences in weight gain	No randomization; no washout period; retrospective evaluation; evaluators not blind to treatment; more frequent side effects in TYP (64%) vs RIS (15%); Benzodiaz-epines more frequent with RIS; anti-parkinsonian meds more frequent in TYP
Ciudad et al 2004 [31]	Prospective quasi-experimental; OLZ: n = 105; RIS/TYP: n = 30	OLZ mean dose 11.7 mg/d OTHER: RIS (n = 15, mean dose 4.2 mg/d) and TYP (n = 15, mean dose not stated)	OLZ: age 65.8 ($\pm$5.9); female 63.8% RIS/TYP: age 65.6 ($\pm$5.3); female 46.7%; Dx, schizophrenia	6 mo; Discontinuation: OLZ, 16%, RIS/TYP, 13%	No differences between OLZ and RIS/TYP in CGI, GAF, EQ-5D, and Awad scores	No randomization; evaluators not blind to treatment; Safety, RIS/TYP more likely to have adverse event than OLZ (72% vs 58%)

Open-label prospective						
Madhus-oodanan et al 1999 [32]	Prospective open-label, multicenter; RIS: n = 103	RIS: Mean dose 2.4 mg/d; most patients (73%) received a mean dose $\leq$ 3 mg/d	Inpatients; age 71 ($\pm$5.4); female: 49.5%; Dx, schizophrenia/ schizoaffective	12-wk study; Discontinuation (25%): adverse events (11), patient choice to discontinue (7), administrative reasons or inadequate response (8)	BPRS and PANSS total and POS, NEG, GEN subscales were improved; clinical improvement, 45% were improved according to criteria of $\geq$20% reduction in PANSS total and a CGI score $\geq$3	No control group; short washout period; high use of concurrent meds; Safety, ESRS scores reduced; no changes in labs, vitals, or EKG
Davidson et al 2000 [33]	Prospective open-label, multicenter; RIS: n = 180	RIS: mean dose 3.7 mg/d	Mean age 73; female 62%; Dx, schizophrenia/ schizoaffective and PANSS 60–120	12-mo; Discontinuation (46%): adverse event (n = 30); insufficient response (n = 26)	Improvement on PANSS total and POS, NEG, and GEN subscales and cognition cluster scores; PANSS clinical improvement achieved by 54% at endpoint; CGI clinical improvement achieved by 59% at endpoint	No control group; Safety, 22% of patients had EPS-like adverse events; no significant weight gain [67]

Abbreviations: Awad, 10-item scale used to evaluate patients attitude toward medication; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression Scale; Dx, diagnosis; EPS, Extrapyramidal symptoms; EQ-5D, European Quality of Life questionnaire; GAF, Global Assessment of Functioning scale; GEN, general; HAL, haloperidol; MADRS, Montgomery-Asberg Depression Rating Scale; NEG, negative; OLZ, olanzapine; PANSS, Positive and Negative Syndrome Scale; POS, positive; QOL, World Health Organization Quality of Life questionnaire; RIS, risperidone; TYP, Typical or conventional antipsychotics.

Augmentation studies

Table 3 describes two RCTs of antidepressant augmentation of antipsychotic agents. The first double-blind, placebo-controlled study has indicated that mianserin and trazodone were associated with improved affective flattening and alogia [34]. In addition, a single-blind RCT of citalopram augmentation has suggested improvements in depression and clinical global impression [35]. Both studies had small sample sizes [34,35], and one study was conducted only among male Veterans Affairs patients [35]. Two recent small pilot studies have evaluated augmentation therapy with donepezil (N = 6) [68] and rivastigmine (N = 13) [69] among persons who had chronic schizophrenia and comorbid dementia and found improvements in cognitive functioning.

Pharmaceutical company support

Of note, all but three of the fourteen pharmacologic studies meeting inclusion criteria were supported by funding from pharmaceutical companies. The studies without pharmaceutical support included the RCT of clozapine and chlorpromazine [24] and the two augmentation studies of antidepressant agents [34,35]. Pharmaceutical support should be considered in evaluating studies because of the potential for conflicts of interest associated with the study design, data analysis, and publication bias [70].

Nonpharmacologic interventions: identification of studies

Among the five evaluations of nonpharmacologic interventions, two studies described results of RCTs [71,72], two studies reported on quasi-experimental studies [73,74], and one study reported on a noncontrolled prospective cohort study [75]. Three promising psychosocial interventions for older adults who had schizophrenia and other psychotic disorders have been developed and described within these reports. These interventions included a combined skills training and cognitive behavioral treatment for middle-aged and older adults who had schizophrenia [71,72,75]; a social skills training program for middle-aged and older adults who had chronic psychotic disorders [73]; and a combined skills training and health management intervention for community-dwelling older adults who had serious mental illness [74]. Each represents a manualized intervention with prospective outcome data. These models are summarized in Table 4.

The modular Cognitive Behavioral Social Skills Training (CBSST) program, consisting of group training in cognitive restructuring and illness self-management skills, was used throughout the program to challenge patients' convictions regarding delusional beliefs and to explore the resistance to treatment recommendations, including medication nonadherence and homework noncompliance. McQuaid and colleagues [75] have described

Table 3
Randomized trials of other psychoactive medications in older adults with schizophrenia

Study	Study design	Agent	Sample	Follow-up	Outcome measures and results	Limitations and comments
Hayashi et al 1997 [34]	Double-blind, RCT; augmentation with MIA, n = 13; TRZ, n = 13; PBO, n = 13	MIA mean dose 58.5 mg/d; TRZ mean dose 192.3 mg/d	Age 62.7; female 39.5%; Dx, schizophrenia with moderate to severe negative symptoms, based on PANSS	5 wk; Discontinued: MIA, 0%; TRZ, 8% (n = 1) for agitation; PBO, 0%	MIA and TRZ improved in affective flattening and blunting and alogia; MIA, SANS total decreased; No differences between MIA and TRZ on SANS scores; TRZ, improved AIMS score; no change in BPRS total, POS factor, or ANX/DEP factor	No severe side effects caused by MIA or TRZ; small sample size; augmentation in addition to a range of conventional antipsychotics
Kasckow et al 2001 [35]	Single-blind RCT; CIT, n = 9; No CIT, n = 10	CIT augmentation starting dose, 20 mg/d; maximal dose did not exceed 40 mg/d	Male veterans; CIT: age, 65.4 ($\pm$12.7) No CIT: age, 59.2 ($\pm$8.2) Dx, chronic schizophrenia and PANSS $\geq$ 45, Ham-D $\geq$ 12	10 wk; Discontinued: CIT, 0%; No CIT, 20%	PANSS total, Ham-D, and CGI improved in both groups; CIT improved more than No CIT in Ham-D and CGI; no change in MMSE	Small sample size; mean dose not reported; no major adverse events; No CIT group did not receive a placebo pill; augmentation to conventional and atypical antipsychotics

Abbreviations: AIMS, abnormal Involuntary Movement Scale; ANX/DEP, anxiety and depression; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression Scale; CIT, citalopram augmentation; Dx, diagnosis; Ham-D, Hamilton Depression Scale; MIA, mianserin; MMSE, mini-mental state examination; PANSS, Positive and Negative Syndrome Scale; PBO, placebo; SANS, scale for the Assessment of Negative Symptoms; TRZ, trazodone.

Table 4
Psychosocial interventions in older adults with schizophrenia

Study	Study design	Model and conditions	Sample	Follow-up	Outcome measures and results	Limitations and comments
McQuaid et al 2000 [75]	Non-controlled, prospective cohort, n = 9	CBSST (12 wk)	Age 62.6 (±8.7); female 22%; Dx, 100% schizophrenia	3 mo; 1 dropped out before groups began	Good attendance and compliance with homework	Small sample size; only 1 assessment tool administered; no data presented on the assessment tool (3-item self-report measure); mostly male participants
Granholm et al 2002 [71]	Single-blind RCT, CBSST, n = 8; TAU, n = 7	CBSST (12 wk) vs TAU	CBSST: age 55.0 (±5.9); female 12.5%; Dx, 100% schizophrenia TAU: age 56.3 (±7.7); female 14.3%; Dx, 100% schizophrenia	3 mo; retention rate not specifically mentioned	Greater reduction in positive and depressive symptoms for CBSST; greater reduction in negative symptoms for TAU	Small sample size; no between-group differences are significant; no age ranges provided; no functional impairment inclusion criterion; mostly male subjects
Patterson et al 2003 [73]	Quasi-experimental, 2 FAST sites, n = 16; 2 TAU sites, n = 16	Skills training (24 wk) in social skills and illness self-management (FAST) vs TAU	FAST: age 47.9 (±5.3); female 31%; Dx, 81% schizophrenia TAU: age 51.7 (±8.5); female 31%; Dx, 69% schizophrenia	9 mo; 20% dropped out after baseline assessment	Greater improvement for FAST in independent living skills and negative symptoms (PANSS); no changes in positive symptoms or quality of well being	Small sample size; no measurement of social functioning; includes patients in their 40s; no functional impairment inclusion criterion

Bartels et al 2004 [74]	Quasi-experimental, ST+HM, n = 12; HM only, n = 12	Skills training in illness self-management and ST + assistance from a nurse (HM) vs HM only for 12 mo	ST+HM: age: 65 (±4.6); female 75%; Dx, 66% schizophrenia; TAU: age 67.9 (±6.4); female 67%; Dx, 66% schizophrenia	ST+HM vs HM (n = 12 vs n = 12) 12 mo; HM (n = 24) 24 mo	Greater improvement for ST+HM in independent living skills and social functioning; HM resulted in identification of previously undetected medical conditions and greater receipt of preventive health care	Small sample size; no TAU comparison; HM only were dropouts from ST+HM; mostly female subjects
Granholm et al 2005 [72]	Single-blind RCT, CBSST, n = 37; TAU, n = 39	Cognitive behavioral therapy + skills training (24 wk) in illness self-management (CBSST) vs TAU	CBSST: age 54.5 (±7.0); female 30%; Dx, 100% schizophrenia TAU: age 53.1 (±7.5); female 23%; Dx, 100% schizophrenia	6 mo; 86% retention	Greater improvement for CBSST in cognitive insight (Beck Cognitive Insight Scale), mastery of skills (Comprehensive Module Test), and leisure skills (Independent Living Skills Survey)	Includes patients in their 40s; No measurement of social functioning; no follow-up beyond post-treatment; no functional impairment inclusion criterion; measure of skill acquisition represents teaching to the task; mostly male subjects

Abbreviations: CBSST, cognitive behavioral therapy plus social skills training; Dx, diagnosis; FAST, Functional Adaptation Skills Training; HM, health management; PANSS, Positive and Negative Syndrome Scale; ST, skills training; TAU, treatment as usual.

an early evaluation of the CBSST intervention. This noncontrolled, prospective cohort study included only nine participants but established the feasibility of recruiting older adults who have schizophrenia to consistently attend the group sessions and actively participate in activities both in and out of the group setting [75]. An early pilot RCT of the CBSST intervention included 15 participants [71]. Although functional outcomes were not reported in this trial, the authors have noted greater reductions in positive and depressive symptoms for the CBSST group compared with the usual care group. More recently, Granholm and colleagues [72] conducted a randomized, controlled trial of the CBSST program that included 76 outpatients who had schizophrenia or schizoaffective disorder ranging in age from 42 to 74 years old. One half of the patients were randomly assigned to receive CBSST and the other half to care as usual. The authors have reported significant improvements in the CBSST group compared with the care as usual group in "social functioning," cognitive insight (insight about beliefs), and performance on a comprehensive module test but no improvements for either group in symptoms, number of hospitalizations, or living skills.

Two quasi-experimental studies of skills training interventions have been conducted by Patterson and colleagues [73], who have described an evaluation of the Functional Adaptation Skills Training (FAST) program, a 24-week modular skills training intervention to improve community functioning in middle-aged and older adults who have chronic psychotic disorders. The FAST intervention includes modules related to medication self-management, social skills, communication skills, organization and planning, transportation, and financial management. Four board-and-care homes were randomly assigned to serve as either intervention or usual care research sites. A total of 32 board-and-care residents aged 42 to 69 years participated in the trial. Positive findings from this study included significantly greater improvement in community functioning skills for the FAST group compared with the care as usual group, both at post-treatment and at 3-month follow-up [73]. There were no significant differences between the groups in the improvement of psychiatric symptoms.

Bartels and colleagues [74] have reported on an evaluation of the Skills Training and Health Management (ST+HM) intervention, which was developed for older adults who have serious mental illness, with the aim of enhancing independent functioning and health care outcomes [74]. A pilot study of the ST+HM intervention included 24 outpatients over the age of 60, of whom two thirds had schizophrenia or schizoaffective disorder and one third had bipolar disorder. Half of the sample received weekly ST focusing on medication self-management and social skills plus assistance from a nurse with accessing preventive and chronic medical care (HM) for 1 year, whereas the other half received HM alone for 1 year. A greater improvement in independent living skills was obtained for individuals who received ST+HM compared with individuals who received only HM. Medium to large effect sizes were found for individuals who received ST+HM compared with

HM alone in several specific skill areas, including self care and health management skills. Compared with those who received HM alone, older adults who received ST+HM also demonstrated a significant improvement in social functioning. Positive findings from the HM component, which all participants received, included the identification of several previously undetected medical conditions in approximately one third of the sample and improvement in the receipt of preventive health care services. An adaptation of the ST+HM model is currently being evaluated in a multisite RCT [76].

Discussion

This review identified 14 studies of pharmacologic trials and five studies of three nonpharmacologic interventions that were evaluated among older adults who had schizophrenia. Published data from RCTs support the effectiveness of antipsychotic medications in the treatment of schizophrenia in older adults, although only modest differences exist between individual antipsychotic agents in effectiveness. Overall, the studies comparing atypical and conventional antipsychotics found modest advantages favoring the effectiveness and lower incidence of parkinsonism for atypical antipsychotics, although similar rates of discontinuation have been reported. The three RCTs comparing the effectiveness of atypical and conventional antipsychotics included two studies that found modest advantages of atypical antipsychotics over conventional antipsychotics [25,28] and one study that found no differences [24]. In addition, less parkinsonism was associated with risperidone and olanzapine compared with conventional antipsychotics [29]. In contrast, no consistent differences were found in the effectiveness and incidence of side effects in an RCT comparing two different atypical antipsychotics. A comparison of risperidone and olanzapine did not detect significant differences in effectiveness in improving psychotic symptoms [26] or cognitive outcomes [27]. In addition to the findings supporting the effectiveness of pharmacologic interventions, a limited literature suggests that nonpharmacologic interventions, particularly skills training, hold promise for enhancing skills required for community functioning.

The largest RCT comparing the effectiveness of two different atypical antipsychotic agents in the treatment of older adults who had schizophrenia includes separate reports on symptom outcomes by Jeste and colleagues [26] and cognitive outcomes by Harvey and colleagues [27]. The 8-week double-blind study randomly assigned 175 persons who had schizophrenia or schizoaffective disorder (ages 60 and older) to receive olanzapine or risperidone. Similar improvements in positive symptoms, negative symptoms, disorganized thoughts, and affective symptoms were found for both groups. Clinical global impression scores also improved in both groups [26]. Evidence for the improvement of attention and memory was obtained for both groups; however, executive function and verbal fluency improved only in the group

receiving risperidone [27]. No change was found in uncontrolled hostility or excitement on the PANSS.

Among the small group of studies that have specifically examined the effectiveness of antipsychotic medications in older adults who had schizophrenia, findings on effective dosages provide some guidance to practicing clinicians. Generally, dosages for older adults who have schizophrenia are approximately twice those recommended in the treatment of older persons who have behavioral symptoms of dementia [77,78]. For example, dosages of approximately 2 mg/d for risperidone and 10 mg/d for olanzapine in older adults who have schizophrenia are twice those reported to be useful in dementia patients (1 mg/d for risperidone and 5 mg/d for olanzapine).

There is no compelling evidence supporting an advantage of any one antipsychotic agent or class of antipsychotic agents over another with respect to discontinuation rates. These rates varied widely across different studies and interventions. Among the pharmacologic studies, 19% to 46% of persons receiving risperidone discontinued treatment before the end of the study [26,27,29,30,32,33]; 12% to 40% of persons receiving olanzapine discontinued treatment before the end of the study [25–29,31]; and 27% to 47% of persons receiving haloperidol discontinued treatment before study completion [23,28]. Among nonpharmacologic studies, dropout rates were only 10% to 20%. However, retention rates for all of these studies should be considered with caution because of small sample sizes and large variations in study duration (6 weeks to 1 year).

There are a small number of differences with respect to the overall incidence of significant side effects between different agents. For example, olanzapine, risperidone, and haloperidol have been associated with weight gain in older adults who have schizophrenia [26,28], although weight gain is most pronounced among patients receiving olanzapine. The study by Jeste and colleagues [26] has noted that clinically relevant weight gain ($\geq$7%) was three times more common among persons receiving olanzapine compared with risperidone, and an open-label study has found no weight gain associated with use of risperidone over 1 year for 127 older persons who had schizophrenia [67]. The US Food and Drug Administration (FDA) has recently issued a warning regarding the association between atypical antipsychotics and the risk for weight gain and diabetes [79,80]. American Diabetes Association and American Psychiatric Association (ADA/APA) guidelines identify different levels of risk of these two adverse effects associated with different atypical antipsychotic agents, with clozapine and olanzapine having the highest risk, followed by quetiapine and risperidone. Aripiprazole and ziprasidone reportedly have the lowest risk, although the data on these two drugs are limited [81].

The only study comparing clozapine (n = 24) to a conventional antipsychotic (n = 18; chlorpromazine augmented with benzotropine) has found no difference in terms of safety or efficacy over a 3-month period, although both agents were associated with significant hematologic events [24]. Although there were no differences with respect to positive and negative

symptoms and global clinical severity, the discontinuation rate was higher in persons receiving chlorpromazine (39% versus 13%). Of note, 33% (8/24) of the patients who received clozapine and 44% (8/18) of those who received chlorpromazine developed hematologic abnormalities [24]. This finding reinforces the need to monitor white blood cell counts for persons receiving these agents. The risk for clozapine-associated agranulocytosis is heightened among older adults (compared with younger adults) and should be closely monitored [55,82]. No other studies have compared clozapine to other agents in this population. One small case study of clozapine use in five older persons who had schizophrenia found improvements in symptoms but also identified substantial side effects, including agranulocytosis, sedation, orthostasis, and worsening of congestive heart failure [40].

To date, there have been no aggregate analyses of serious adverse events, including mortality across multiple studies of atypical antipsychotics in older persons who had schizophrenia. Of note, the FDA has recently issued a warning regarding the use of all atypical antipsychotic agents in older adults who have dementia. Fifteen of seventeen placebo-controlled studies of olanzapine, risperidone, quetiapine, and aripiprazole have shown numerical increases in mortality, compared with placebo, for older adults who had behavioral disorders of dementia. These studies involved 5106 patients and identified mortality rates of 4.5% among patients who received atypical antipsychotics, compared with 2.6% among those who received placebo ($P < .05$). These data demonstrate a 1.6 to 1.7 fold increase in mortality, most commonly caused by cardiovascular events or infections such as pneumonia [83,84]. Because these studies were almost entirely populated by elderly persons (including many with psychotic symptoms), a systematic evaluation of serious adverse events in older adults who have schizophrenia receiving atypical antipsychotics is indicated.

The current findings on augmentation therapy are suggestive but not definitive with respect to the potential benefits of adding antidepressants or cholinesterase inhibitors to antipsychotic medications. For example, Hayashi and colleagues [34] have found that trazodone and mianserin were associated with a reduction in negative symptoms (affective flattening or blunting and alogia). Trazodone was also associated with decreased EPS. However, neither treatment was associated with an improvement in psychotic symptoms or affective symptoms [34]. In contrast, Kasckow and colleagues [35] have reported that older adults receiving citalopram augmentation had significantly greater improvement in depressive symptoms and clinical global severity, compared with a control group. Augmentation with cholinesterase inhibitors was evaluated in two small case series of patients who had schizophrenia and comorbid dementia [68,69]. Stryer and colleagues [68] conducted a 4-week single-blind administration of donepezil (5 mg/d) augmentation for six patients. Significant improvements were seen in cognitive impairment and Clinical Global Impression Scale scores. Similarly, Mendelsohn and colleagues [69] conducted a 12-week open-label

examination of 13 patients who received rivastigmine augmentation (9 mg/d). Improvements were seen in cognitive impairment, activities of daily living, and negative symptoms. These open-label studies give preliminary evidence supporting cholinesterase inhibitors in improving cognitive symptoms among persons who have comorbid dementia and schizophrenia. In addition, as shown by the RCT conducted by Harvey and colleagues [27], olanzapine and risperidone may also positively affect cognitive functioning in some older persons who have schizophrenia. At this stage, however, the value of these drugs in improving cognition in schizophrenia is unclear.

There are several limitations to the evidence base for the pharmacologic treatment of older adults who have schizophrenia. First, there are few well-designed head-to-head comparisons of antipsychotic agents or psychosocial interventions. Second, to our knowledge, no studies have evaluated the cost effectiveness of any treatment modality for older adults who have schizophrenia. Third, only five of 14 studies have evaluated long-term effects ($\geq$3 months), tolerability, or safety of pharmacologic interventions [23,28,30,31,33]. In contrast, psychosocial interventions have been evaluated over a period of 3 months to 1 year [71–75]. This difference is, in part, associated with the progressive learning approach used in the skills training interventions. Fourth, clinical trials of antipsychotic medications among older adults who had schizophrenia have often been limited by small sample sizes and inadequate control over doses, duration of treatment, and concomitant medications. Finally, little is known about the effectiveness or safety of newer antipsychotics such as quetiapine, ziprasidone, or aripiprazole among older adults who have schizophrenia or schizoaffective disorder. Quetiapine was approved for use among persons who have schizophrenia by the FDA in 1997, but limited research has evaluated its effectiveness and safety among older adults. One small pilot study has evaluated quetiapine among six older persons (ages 61–72) who had schizophrenia or schizoaffective disorder [45]. Three patients experienced reductions in positive and negative symptoms. Pre-existing EPS decreased in three of five persons; transient hypotension, dizziness, and somnolence developed in two patients; and patient weight increased by an average of 2 pounds [45]. A larger mixed-sample study (N = 151) has evaluated the effectiveness of quetiapine in older adults who had psychotic disorders. This study focused on older individuals with Alzheimer's and Parkinson's disease but did not specifically report outcomes on the smaller sample with schizophrenia (N = 33) [46]. Aripiprazole (approved by the FDA in 2002) has been evaluated in a recent case study of 10 hospitalized older adults who had schizophrenia or schizoaffective disorder (ages 62–85). Seven of 10 patients responded to aripiprazole and showed improvements in positive and negative symptoms as well as global clinical impression. Pre-existing EPS decreased in three of four patients, and four of 10 patients developed postural hypotension that resolved over time. Six of the 10 patients lost an average of 5.25 pounds, although one patient gained 18 pounds [38]. This preliminary evidence suggests that quetiapine

and aripiprazole may be similar to other atypical antipsychotics in effectiveness and safety among older adults who have schizophrenia and schizoaffective disorder. To our knowledge, there are no published reports on the effectiveness or safety of ziprasidone (approved by the FDA in 2001) in the treatment of older adults who have schizophrenia. Further evaluation of these agents is warranted.

Compared with pharmacologic trials, the evaluation of psychosocial interventions for older persons who have schizophrenia has been even more limited. Several interventions have been developed that have been specifically tailored to improve functioning in aging individuals with schizophrenia. These interventions have been manualized and delivered in community settings with mental health consumers. The interventions were well tolerated, had low dropout rates, and were associated with positive outcomes. Nevertheless, several caveats are in order. First, sample sizes in the evaluations of these interventions were very small, in which four of the five studies included fewer than 35 participants [71,73–75]. Second, four of the five studies described interventions for "middle-aged and older adults" and included individuals as young as age 42 [71–73,75]. Finally, two of the five studies included diagnoses other than schizophrenia [73,74]. Although a majority of these samples consisted of persons who had schizophrenia, subanalyses of individuals with schizophrenia alone were not conducted. Overall, it is likely that older adults can tolerate psychosocial interventions and benefit from them, although larger randomized trials are needed to establish effectiveness.

This review examines the evidence base for pharmacologic and nonpharmacologic interventions that have been evaluated among older adults who have schizophrenia. Because of age-related differences in medical comorbidity, stressors, cognitive function, and other factors, pharmacologic and psychosocial interventions for older adults who have schizophrenia are different from those used for treating younger adults. Although several database studies support the use of medications and psychosocial interventions to improve the psychiatric symptoms and functioning of older persons who have schizophrenia, to date there has been a lack of rigorous evaluation for many of the newer antipsychotic agents, and few nonpharmacologic interventions have been developed or evaluated. Furthermore, many of the published reports have methodological limitations and potential difficulties with generalizability. Despite these limitations, this review identifies the evidence base for both classes of interventions and shows that older adults can improve with pharmacologic and psychosocial interventions. Further research conducted through well-designed studies is needed to identify optimal treatments for different subgroups of older persons who have schizophrenia.

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