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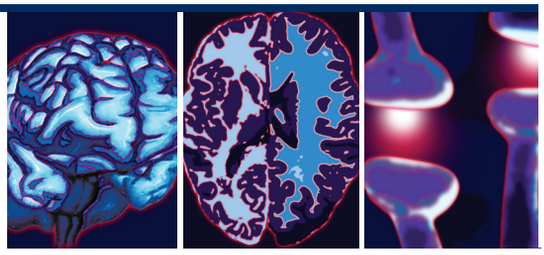

Treatment-refractory schizophrenia: what is it and what has been done about it?

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Practice points

- Treatment-refractoriness is commonly encountered among patients with schizophrenia.
- When psychotic symptoms appear to be persistent, poor adherence and/or use of a suboptimal dose of antipsychotic medication needs to be ruled out.
- Among the antipsychotic monotherapies, clozapine has consistently demonstrated more robust treatment effect sizes compared with first-generation antipsychotics.
- Antipsychotic combination therapy has not been shown to be substantially superior to antipsychotic monotherapy.
- Adjunctive use of nonantipsychotic medications have not consistently demonstrated superior outcomes compared with antipsychotic monotherapy, but data regarding antidepressant use for negative symptoms appears promising.
- Although current efforts to address cognitive dysfunction by pharmacological means have so far generally resulted in disappointing results, agents that impact glutamate receptors are being actively studied in many randomized controlled studies.
- Several adjunctive nonpharmacological interventions may be helpful, including cognitive behavioral therapy.

SUMMARY There has been a veritable explosion of research conducted for interventions that may be advantageous for the management of treatment-refractory schizophrenia. After a discussion of how to define treatment resistance or treatment refractoriness, obstacles to its accurate identification are presented. Randomized clinical trials that have tested antipsychotic monotherapies, antipsychotic combination therapies, nonantipsychotic augmentation strategies and nonpharmacological interventions are catalogued. Although clozapine has been a landmark medication, attempts to augment it have not resulted in any further breakthroughs of the same magnitude. Some logical candidates for augmentation have not been successful, including anticholinesterase inhibitors and other agents used to

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treat cognitive decline in Alzheimer's disease. Antipsychotic combinations have resulted in incremental improvements at best. Research being done with antidepressant medications and with agents that impact on the glutamate receptor holds the greatest promise at this time.

Schizophrenia is a chronic psychotic disorder with a complex natural history [1]. Although individuals with schizophrenia usually experience their first psychotic episode in late adolescence or early adulthood, subsequent episodes are the norm, particularly if the course of treatment with antipsychotics is interrupted. After each psychotic episode, more time is required before functional recovery can occur, with treatment response becoming less robust [2]. Furthermore, prolonged duration of untreated psychosis prior to the initiation of treatment is associated with poorer symptomatic and functional recovery in initial episodes [3]. Thus clinical practice is replete with patients with schizophrenia who appear partially responsive or refractory to treatment with antipsychotic medication.

A search of PubMed on 11 February 2010 on the text words 'augmentation' or 'adjunctive' or 'treatment refractory' or 'treatment resistant' and 'schizophrenia' yielded 1575 citations, of which 236 were categorized as randomized controlled trials in human subjects with results reported in English. Upon inspection, not all of these reports were relevant to the clinical management of patients with treatment-refractory schizophrenia. Additional studies were identified by examining reference lists and the author's own reprint library. A caveat is that 'negative' studies may have been completed but never published. This review provides a summary of the pertinent efficacy evidence base, together with an overview of how treatment resistance can be defined as well as a general clinical approach to this problem.

How is treatment-refractory schizophrenia defined?

Treatment refractoriness is in the eye of the beholder. Research definitions have attempted to operationally define treatment-refractory schizophrenia in order to test potential interventions. For example, the classic randomized controlled trial evaluating clozapine included the following criteria:

- At least three periods of treatment in the preceding 5 years with neuroleptic agents (from at least two different chemical classes) at dosages equivalent to or greater than 1000 mg/day of chlorpromazine for a period of 6 weeks, each without significant symptomatic relief;
- No period of good functioning within the preceding 5 years [4].

Furthermore, a prospective period of treatment with haloperidol (up to 60 mg/day or higher) and benztropine mesylate (6 mg/day) for a period of 6 weeks to confirm the lack of drug responsiveness was also part of the study design. More than a decade later, more relaxed criteria were used to test interventions in patients with schizophrenia with a history of suboptimal treatment response [5]. This was defined as persistent positive symptoms (hallucinations, delusions or marked thought disorder) after at least 6 contiguous weeks of treatment, presently or documented in the past, with one or more typical antipsychotics at doses of at least 600 mg/day in chlorpromazine equivalents, and a poor level of functioning over the past 2 years, as defined by the lack of competitive employment or enrollment in academic or vocational programs and not having age-expected interpersonal relations with someone outside the biological family of origin with whom ongoing regular contacts were maintained. No prospective period of treatment to confirm lack of drug responsiveness was required. Thus research criteria for treatment-refractory schizophrenia can differ and has evolved over time.

Clinicians have become more aware of the multiple dimensions of schizophrenia and lack of treatment response can be either global or restricted to a specific domain. Positive and negative symptoms of schizophrenia are well recognized and can be described using rating scales such as the Positive and Negative Syndrome Scale (PANSS) [6]. The PANSS has also been analyzed using 5-factor models that have identified the independent domains of positive, negative, excitement, cognitive and depression/anxiety factors [7]. For some patients, targeting positive symptoms is a high priority, for others it may be negative and cognitive symptoms, and for others, it may be excitement. Different antipsychotics may be preferable depending on

the specific target symptoms [8], with perhaps the best example being clozapine's efficacy in hostility, aggression and violent behavior [9].

Functional impairment can be another focus of treatment and although functional impairment can be driven by symptoms, it has been observed that 5–17% of patients who experience functional recovery do not show symptomatic remission [10]. Different assessment tools are available for psychosocial functioning, including the Personal and Social Performance scale [11], the Schizophrenia Outcomes Functioning Interview [12], the University of California, San Diego (UCSD; CA, USA) Performance-based Skills Assessment [13] and several others [10].

Definitions for remission and functional recovery are in flux, although operationalized criteria for symptomatic remission have been published [14] and have been used for research purposes [15]. Essentially, symptomatic remission can be defined as the maintenance over a 6-month period of simultaneous ratings of mild or less on delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior and negative symptoms. Emsley and colleagues note that reported remission rates vary widely across studies (17–88%) and that patients in remission do better than their nonremitted counterparts in several other outcome domains [15]. They note several predictors of remission: early treatment response, baseline symptom severity and subjective well-being. They also note that patients move in and out of remission over time. Recovery is a more complex construct than remission and includes social outcomes, such as the ones described in the prior paragraph. Despite the lack of a standard definition for recovery, it is the implied goal of treatment. Anything short of recovery can be viewed as inadequate. Whether treated patients with schizophrenia, who have not reached recovery, should all be classified as treatment-refractory is open to debate.

Obstacles to accurately identifying treatment nonresponse

Nonadherence with antipsychotic treatment is common, and is associated with relapse and rehospitalization [16]. Nonadherence has been estimated to occur in approximately half of patients being treated for schizophrenia [17]. Factors related to poor adherence include lack of insight, tolerability issues, access to treatment, substance use, cognitive deficits, negative symptoms, poor therapeutic alliance and inadequate external supports [17,18]. The lack of insight is very common among patients with schizophrenia with approximately 50% of patients at least partially lacking insight into their illness [19]. Furthermore, it has been estimated that approximately half of all individuals with schizophrenia also abuse alcohol and illegal drugs [20]. It is thus not surprising that treatment refractoriness can be inappropriately used to label a patient who is actually nonadherent and perhaps using illicit substances. This misidentification can be especially common when the patient with schizophrenia is covertly noncompliant.

Use of an inadequate dose of an antipsychotic can lead to the premature declaration that the patient does not respond to that medication. This can occur when information regarding the optimal dose is unknown or not well promulgated. Dosing ranges established during registration studies may not reflect the needs of day-to-day clinical practice [21], hence it is not unexpected that some patients may be categorized as treatment refractory when in fact they have not received an adequate antipsychotic dose for an adequate period of time.

Patient perspectives & preferences

As noted, patients with schizophrenia can have limited insight into their psychotic symptoms. However, patients can retain insight in other ancillary symptoms, such as impaired sleep, anxiety and dysphoria. From a patient perspective, a medication that has reduced the intensity and frequency of auditory hallucinations and delusions, but that has not alleviated poor sleep, anxiety or dysphoria will be considered by the patient as unhelpful to them. This can lead to nonadherence, eventual worsening of the psychotic symptoms and the mistaken belief on the part of the clinician that the patient is refractory to treatment.

What is the evidence base for different interventions?

■ Monotherapies

Assuming that a medication is dosed correctly and given over an adequate period of time and that a reasonable degree of adherence can be established, are there any differences among the antipsychotic monotherapies in terms of efficacy? This question has been addressed using

meta-analytic techniques whereby results from randomized controlled trials are pooled together and treatment effect size differences are calculated. Three 'tiers' of antipsychotic medications become evident [22–24]:

- Clozapine is in a class by itself, with general efficacy advantages over other antipsychotics;
- Olanzapine, risperidone, and amisulpride, which appear to have efficacy advantages over first-generation antipsychotics;
- The other remaining second-generation and first-generation antipsychotics, which are not differentiable in terms of efficacy (although their tolerability profiles can vary greatly).

Clozapine's advantages over risperidone and quetiapine (but not olanzapine) were also evident in an effectiveness study, where time to all-cause discontinuation was the primary outcome measure [25], and consistent with a prior efficacy study comparing clozapine, olanzapine, risperidone and haloperidol [5]. **Table 1 & Supplementary Table 1** (see online at www.futuremedicine.com/doi/suppl/10.2217/npy.11.35) outline several studies [4,5,25–58] of antipsychotic monotherapies where treatment-refractory patients were the focus of attention (excluded are studies that examined different doses or plasma levels of the same medication). Although the bulk of the studies are for adult patients with schizophrenia, there are studies that have examined childhood-onset treatment-refractory schizophrenia as well [28,51,53]. For the most part, clozapine has consistently demonstrated superiority over comparators. Because not all patients with schizophrenia can tolerate clozapine or are willing to have their blood monitored as required, other second-generation antipsychotics have been suggested as possible substitutes for clozapine [5,33–58]. Olanzapine is one such second-generation antipsychotic that has established superior efficacy to first-generation antipsychotics [22–24] and perhaps comparable to clozapine in some studies [5,25,46,49,52]. Although risperidone also appears to be comparable to clozapine in some studies [34,39], superiority of clozapine was evident in others [25,38,40], and thus the evidence is more consistently in favor of olanzapine in treatment-refractory schizophrenia rather than using risperidone in this population. Although favorable results were also observed for ziprasidone in a randomized clinical trial versus clozapine, patients enrolled were not necessarily treatment refractory *per se* and may have been intolerant to prior treatments [56]. This also complicates the interpretation of one of the studies comparing olanzapine and clozapine [49] and one comparing risperidone with clozapine [34].

Limitations to the aforementioned studies include the restrictive inclusion/exclusion criteria of the individual clinical trials that do not necessarily make it easy to generalize the results to the treatment-refractory patients treated in day-to-day clinical practice. Moreover, individual 'outliers' are commonly encountered in clinical practice whereby a medication that is considered inferior may actually be the optimal selection for that individual in the clinic. This heterogeneity in treatment response is the principal justification for having a variety of antipsychotic medications in a drug formulary [59].

Antipsychotic combinations

Combinations of antipsychotics are commonly used, particularly among patients with schizophrenia who are served in public health systems and who have been ill for several years [60], with doses that do not differ substantially from those given as monotherapies [61]. **Table 2 & Supplementary Table 2** outline several randomized controlled trials of antipsychotic combinations [62–81], most testing combinations that include clozapine [62–76]. There are relatively few studies that actually support the use of antipsychotic combination treatment [63,64,72,75,81], and for the most commonly studied combinations, such as clozapine and risperidone, several negative or equivocal studies have also been published [65–69]. As noted in a Cochrane systematic review [82], problems with small sample size, heterogeneity of comparisons, flaws in the design, conduct and analysis make it difficult to determine which antipsychotic is the best choice to add to clozapine. In their plain language narrative the authors noted that "When people on clozapine plus risperidone were compared with those on clozapine plus sulpiride, more people taking risperidone showed an improvement generally. However, when specific symptoms of schizophrenia were studied, there was change for the better in all groups but no second antipsychotic was significantly better than the one it was compared with. When looking at adverse effects, people taking sulpiride were slightly more likely to suffer from hypersalivation and weight gain than those taking risperidone … Although there is a suggestion that adding a second

Table 1. Antipsychotic medication monotherapies in patients with treatment-refractory schizophrenia as tested in randomized controlled trials.

Study (year)	Duration (weeks)	n†	Monotherapy	Comparator	Ref.
Kane *et al.* (1988)	6	268	Clozapine	Chlorpromazine	[4]
Pickar *et al.* (1992)	Varies	21	Clozapine	Fluphenazine or placebo	[26]
Breier *et al.* (1994)	10	39	Clozapine	Haloperidol	[27]
Kumra *et al.* (1996)	6	21	Clozapine	Haloperidol	[28]
Hong *et al.* (1997)	12	40	Clozapine	Chlorpromazine	[29]
Rosenheck *et al.* (1997)	1 year	423	Clozapine	Haloperidol	[30]
Buchanan *et al.* (1998)	10	75	Clozapine	Haloperidol	[31]
Kane *et al.* (2001)	29	71	Clozapine	Haloperidol	[32]
Volavka *et al.* (2002); Bilder *et al.* (2002)	14	157	Clozapine, olanzapine or risperidone	Haloperidol	[5,33]
McEvoy *et al.* (2006)	NA	99	Clozapine	Olanzapine, risperidone or quetiapine	[25]
Bondolfi *et al.* (1998)	8	86	Risperidone	Clozapine	[34]
Wirshing *et al.* (1999); Kern *et al.* (1999); Green *et al.* (1997)	8	67	Risperidone	Haloperidol	[35–37]
Breier *et al.* (1999)	6	29	Risperidone	Clozapine	[38]
Wahlbeck *et al.* (2000)	10	19	Risperidone	Clozapine	[39]
Azorin *et al.* (2001)	12	273	Risperidone	Clozapine	[40]
Zhang *et al.* (2001)	12	78	Risperidone	Haloperidol	[41]
Liberman *et al.* (2002)	8	36	Risperidone	Haloperidol	[42]
Conley *et al.* (2005)	12	38	Risperidone or quetiapine	Fluphenazine	[43]
Conley *et al.* (1998)	6	84	Olanzapine	Chlorpromazine	[44]
Breier *et al.* (1999)	6	526	Olanzapine	Haloperidol	[45]
Tollefson *et al.* (2001)	18	180	Olanzapine	Clozapine	[46]
Conley *et al.* (2003); Kelly *et al.* (2003)	8 (total 16)	13	Olanzapine	Clozapine	[47,48]
Bitter *et al.* (2004)	18	147	Olanzapine	Clozapine	[49]
Buchanan *et al.* (2005)	16	63	Olanzapine	Haloperidol	[50]
Shaw *et al.* (2006)	8	25	Olanzapine	Clozapine	[51]
Meltzer *et al.* (2008)	6 months	40	Olanzapine	Clozapine	[52]
Kumra *et al.* (2008)	12	39	Olanzapine	Clozapine	[53]
Emsley *et al.* (2000)	8	288	Quetiapine	Haloperidol	[54]
Kane *et al.* (2006)	12	306	Ziprasidone	Chlorpromazine	[55]
Sacchetti *et al.* (2009)	18	147	Ziprasidone	Clozapine	[56]
Kane *et al.* (2007)	6	300	Aripiprazole	Perphenazine	[57]
Lal *et al.* (2006)	14	38	Levomepromazine	Chlorpromazine	[58]

All studies are double blind and parallel group unless otherwise noted (see **Supplementary Table 1** for further details).
†Randomized.
NA: Not applicable.

antipsychotic may improve general functioning and decrease the symptoms of schizophrenia, it is still not possible to say which antipsychotic would help the most" [82].

■ Adjunctive nonantipsychotic medications

Adjunctive nonantipsychotic medications are also commonly used when treating patients with schizophrenia. For example, lithium and anticonvulsants are used in approximately half of all patients with schizophrenia hospitalized in facilities operated by the State of New York Office of Mental Health [83,84]. The evidence base for these agents as adjuncts to antipsychotics is generally weak [85]. Specifically, early reports of the usefulness of lithium as an adjunctive agent have been negated by later studies. Similarly, large trials of adjunctive valproate and adjunctive lamotrigine completed in the wake of early and promising efficacy signals from smaller studies have failed to replicate the initial findings, although the larger studies did not specifically

Table 2. Antipsychotic medication combinations in patients with schizophrenia as tested in randomized controlled trials, with an emphasis on treatment-refractory schizophrenia.

Study (year)	Duration (weeks)	n[†]	Combination	Comparator	Useful?[‡]	Ref.
Potter *et al.* (1989)	8	57	Chlorpromazine and clozapine	Clozapine or chlorpromazine	Maybe	[62]
Shiloh *et al.* (1997)	10	28	Sulpiride and clozapine	Clozapine	Yes	[63]
Josiassen *et al.* (2005)	12	40	Risperidone and clozapine	Clozapine	Yes	[64]
Anil Yağcioğlu *et al.* (2005); Akdede *et al.* (2006)	6	30	Risperidone and clozapine	Clozapine	No	[65,66]
Honer *et al.* (2006)	8	68	Risperidone and clozapine	Clozapine	No	[67]
Freudenreich *et al.* (2007)	6	24	Risperidone and clozapine	Clozapine	Maybe	[68]
Weiner *et al.* (2010)	16	69	Risperidone and clozapine	Clozapine	Maybe	[69]
Kreinin *et al.* (2006)	3 (total 7)	20	Amisulpride and clozapine	Clozapine	Maybe	[70]
Assion *et al.* (2008)	6	16	Amisulpride and clozapine	Clozapine	Maybe	[71]
Genç *et al.* (2007)	8	56	Amisulpride and clozapine	Quetiapine and clozapine	Yes	[72]
Chang *et al.* (2008)	8	62	Aripiprazole and clozapine	Clozapine	Maybe	[73]
Fleischhacker *et al.* (2010)	16	207	Aripiprazole and clozapine	Clozapine	Maybe	[74]
Muscatello *et al.* (2011)	24	40	Aripiprazole and clozapine	Clozapine	Yes	[75]
Zink *et al.* (2009)	6	24	Ziprasidone and clozapine	Clozapine and risperidone	No	[76]
Kane *et al.* (2009)	16	323	Risperidone or quetiapine and aripiprazole	Risperidone or quetiapine	No	[77]
Henderson *et al.* (2009)	4 (total 10)	15	Aripiprazole and olanzapine	Olanzapine	No	[78]
Shafti *et al.* (2009)	12	28	Fluphenazine decanoate and olanzapine	Olanzapine	Maybe	[79]
Kotler *et al.* (2004)	8	17	Sulpiride and olanzapine	Olanzapine	Maybe	[80]
Takahashi *et al.* (1999)	8	8 (total 24)	Risperidone or mosapramine and one or more first-generation antipsychotics	One or more first-generation antipsychotics	Yes	[81]

All studies are double blind and parallel group unless otherwise noted (see **Supplementary Table 2** for further details).
[†]Randomized.
[‡]Usefulness is summarized by: Yes, there is an efficacy signal for at least some of the important efficacy outcomes for the combination treatment versus the comparator, and can serve as justification to conduct another trial; No, no evidence for efficacy and/or worsening with combination treatment; or maybe.

target treatment-resistant schizophrenia. Of all of these 'mood stabilizers,' lamotrigine may be the most promising for treatment-resistant schizophrenia. In a meta-analysis specifically examining clozapine patients (n = 161) who had been randomized to receive either adjunctive lamotrigine or adjunctive placebo, lamotrigine was superior to placebo augmentation in total score for symptoms of psychosis and scores for positive and negative symptoms [86].

Table 3 & Supplementary Table 3 outline several randomized controlled trials of other adjunctive nonantipsychotic medications (excluding agents such as metformin administered to address metabolic variables; for a review of adjunctive metformin and other agents for weight gain see [87]). For many adjunctive strategies the intent is to reduce specific symptoms such as cognitive dysfunction or negative symptoms rather than augment the general antipsychotic effect of the prescribed antipsychotic. Studies listed in **Table 3 & Supplementary Table 3** include acetylsalicylic acid and nonsteroidal anti-inflammatory agents [88–92], antidepressants [93–128], anti-glucocorticoids [129,130], agents used to treat attention-deficit disorder [131–134], β-blockers [135,136], cholinesterase inhibitors and other agents used to treat Alzheimer's disease [137–156], GABA-A receptor drugs [157,158], experimental agents that act on glutamate receptors [159–176], neurosteroids and hormones [177–187], omega-3 fatty acids [188,189], opioid system agents [190–192], peptides [193,194], purinergic agents [195–199], serotonin 5-HT_{1A} receptor agonists [200–203], serotonin 5-HT_{3} receptor antagonists [204,205], wakefulness promoting agents [206–209], and others [210–221].

Of particular interest is the question of adjunctive antidepressant use, for which many randomized controlled studies are available, including tricyclic and tetracyclic antidepressants [93–98,120,121], serotonin-specific reuptake inhibitors [99–112,122,127], monoamine oxidase inhibitors [125,126], mirtazapine [113–119], reboxetine [123], ritanserin [124] and trazodone [128]. When interpreting individual studies, care must be taken regarding the types of patients recruited

Table 3. Antipsychotic medication plus adjunctive nonantipsychotic medication in patients with schizophrenia as tested in randomized controlled trials, with an emphasis on persistent symptoms despite antipsychotic treatment.

Study (year)	Duration (weeks)	n[†]	Combination	Comparator	Useful?[‡]	Ref.
Acetylsalicylic acid and nonsteroidal anti-inflammatory agents						
Müller *et al.* (2002)	5	50	Celecoxib and risperidone	Risperidone	Yes	[88]
Rapaport *et al.* (2005)	8	38	Celecoxib and olanzapine or risperidone	Olanzapine or risperidone	No	[89]
Akhondzadeh *et al.* (2007)	8	60	Celecoxib and risperidone	Risperidone	Yes	[90]
Müller *et al.* (2010)	6	49	Celecoxib and amisulpride	Amisulpride	Yes	[91]
Laan *et al.* (2010)	3 months	70	Aspirin and antipsychotic	Antipsychotic	Maybe	[92]
Antidepressants						
Siris *et al.* (1987)	6	33	Imipramine and fluphenazine decanoate	Fluphenazine decanoate	Yes	[93]
Kramer *et al.* (1989)	4	66	Amitriptyline or desipramine and haloperidol	Haloperidol	No	[94]
Siris *et al.* (1990)	NA	14	Imipramine and fluphenazine decanoate	Fluphenazine decanoate	Yes	[95]
Siris *et al.* (1991)	6 or 9	27	Imipramine and fluphenazine decanoate	Fluphenazine decanoate	Yes	[96]
Siris *et al.* (1992)	6 or 9	21	Imipramine and fluphenazine decanoate	Fluphenazine decanoate	Yes	[97]
Siris *et al.* (1994)	NA	24	Imipramine and fluphenazine decanoate	Fluphenazine decanoate	Yes	[98]
Vartiainen *et al.* (1995)	24 (total 48)	19	Citalopram and antipsychotic	Antipsychotic	Yes	[99]
Salokangas *et al.* (1996); Taiminen *et al.* (1997)	12	90	Citalopram and antipsychotic	Antipsychotic	Maybe	[100,101]
Kasckow *et al.* (2001)	10	19	Citalopram and antipsychotic	Antipsychotic	Yes	[102]
Friedman *et al.* (2005)	12 (total 24)	19	Citalopram and second-generation antipsychotic	Second-generation antipsychotic	No	[103]
Zisook *et al.* (2009); Zisook *et al.* (2010); Kasckow *et al.* (2010)	12	198	Citalopram and one or more antipsychotics	One or more antipsychotics	Yes	[104–106]
Iancu *et al.* (2010)	10	40	Escitalopram and antipsychotic	Antipsychotic	No	[107]
Spina *et al.* (1994)	12	34	Fluoxetine and one or more antipsychotics	One or more antipsychotics	Yes	[108]
Buchanan *et al.* (1996)	8	33	Fluoxetine and clozapine	Clozapine	No	[109]
Silver *et al.* (1992)	5	30	Fluvoxamine and antipsychotic	Antipsychotic	Yes	[110]
Silver *et al.* (2000)	6	53	Fluvoxamine and one or more antipsychotics	One or more antipsychotics	Yes	[111]
Chaichan *et al.* (2004)	6	20	Fluvoxamine and olanzapine	Olanzapine	Yes	[112]
Berk *et al.* (2001)	6	30	Mirtazapine and haloperidol	Haloperidol	Yes	[113]
Zoccali *et al.* (2004)	8	24	Mirtazapine and clozapine	Clozapine	Yes	[114]
Berk *et al.* (2009)	6	40	Mirtazapine and clozapine, quetiapine, risperidone, olanzapine or aripiprazole	Clozapine, quetiapine, risperidone, olanzapine or aripiprazole	No	[115]
Joffe *et al.* (2009); Stenberg *et al.* (2010)	6	41	Mirtazapine and one or more first-generation antipsychotics	One or more first-generation antipsychotics	Yes	[116,117]
Abbasi *et al.* (2010)	8	40	Mirtazapine and risperidone	Risperidone	Yes	[118]

All studies are double blind and parallel group unless otherwise noted (see **Supplementary Table 3** for further details).
For information on anticonvulsants and lithium see [85].
[†]Randomized.
[‡]Usefulness is summarized by: Yes, there is an efficacy signal for at least some of the important efficacy outcomes for the combination treatment versus the comparator, and can serve as justification to conduct another trial; No, no evidence for efficacy and/or worsening with combination treatment; or maybe.
DHEA: Dehydroepiandrosterone; NA: Not applicable.

Table 3. Antipsychotic medication plus adjunctive nonantipsychotic medication in patients with schizophrenia as tested in randomized controlled trials, with an emphasis on persistent symptoms despite antipsychotic treatment (cont.).

Study (year)	Duration (weeks)	n†	Combination	Comparator	Useful?‡	Ref.
Antidepressants (cont.)						
Cho *et al.* (2011)	8	21	Mirtazepine and risperidone	Risperidone	Yes	[119]
Shiloh *et al.* (2002)	6	18	Mianserin and haloperidol or perphenazine	Haloperidol or perphenazine	Yes	[120]
Poyurovsky *et al.* (2003)	4	30	Mianserin and haloperidol, chlorpromazine or perphenazine	Haloperidol, chlorpromazine or perphenazine	Yes	[121]
Jockers-Scherübl *et al.* (2005)	12	29	Paroxetine and antipsychotic	Antipsychotic	Yes	[122]
Schutz *et al.* (2001)	6	30	Reboxetine and haloperidol	Haloperidol	No	[123]
Akhondzadeh *et al.* (2008)	8	40	Ritanserin and risperidone	Risperidone	Yes	[124]
Bodkin *et al.* (2005)	12	67	Selegiline and antipsychotic	Antipsychotic	Yes	[125]
Amiri *et al.* (2008)	8	40	Selegiline and risperidone	Risperidone	Yes	[126]
Lee *et al.* (1998)	8	38	Sertraline and haloperidol	Haloperidol	No	[127]
Decina *et al.* (1994)	6	49	Trazodone and antipsychotic	Antipsychotic	Yes	[128]
Antiglucocorticoids						
Marco *et al.* (2002)	4	15	Ketoconazole and antipsychotic	Antipsychotic	Maybe	[129]
Gallagher *et al.* (2005)	1 (total 6)	20	Mifepristone and antipsychotic	Antipsychotic	No	[130]
Attention-deficit disorder agents						
Carpenter *et al.* (1992)	5 days (total 2 weeks)	8	Methylphenidate and antipsychotic	Antipsychotic	No	[131]
Friedman *et al.* (2001)	4	39	Guanfacine and antipsychotic	Antipsychotic	No	[132]
Friedman *et al.* (2008)	8	20	Atomoxetine and risperidone, olanzapine, quetiapine or aripiprazole	Risperidone, olanzapine, quetiapine or aripiprazole	No	[133]
Kelly *et al.* (2009)	8	32	Atomoxetine and second-generation antipsychotic	Second-generation antipsychotic	No	[134]
β-blockers						
Allan *et al.* (1996)	3	34	Nadolol and first-generation antipsychotic	First-generation antipsychotic	Maybe	[135]
Caspi *et al.* (2001)	6 (total 12)	30	Pindolol and antipsychotic	Antipsychotic	Yes	[136]
Cholinesterase inhibitors and other agents used in Alzheimer's disease						
Friedman *et al.* (2002)	12	36	Donepezil and risperidone	Risperidone	No	[137]
Stryjer *et al.* (2004)	8 (total 18)	8	Donepezil and clozapine	Clozapine	No	[138]
Tuğal *et al.* (2004)	6 (total 12)	12	Donepezil and fluphenazine or pimozide	Fluphenazine or pimozide	No	[139]
Erickson *et al.* (2005)	8 (total 18)	15	Donepezil and one or more antipsychotics	One or more antipsychotics	Yes	[140]
Freudenrich *et al.* (2005)	8	36	Donepezil and one or more antipsychotics	One or more antipsychotics	No	[141]
Mazeh *et al.* (2006)	12 (total 24)	20	Donepezil and antipsychotic	Antipsychotic	No	[142]
Fagerlund *et al.* (2007)	4 months	21	Donepezil and ziprasidone	Ziprasidone	No	[143]
Lee *et al.* (2007)	12	24	Donepezil and haloperidol	Haloperidol	Maybe	[144]
Risch *et al.* (2007)	12	13	Donepezil and olanzapine, risperidone or clozapine	Olanzapine, risperidone or clozapine	Yes	[145]

All studies are double blind and parallel group unless otherwise noted (see **Supplementary Table 3** for further details).
For information on anticonvulsants and lithium see [85].
†Randomized.
‡Usefulness is summarized by: Yes, there is an efficacy signal for at least some of the important efficacy outcomes for the combination treatment versus the comparator, and can serve as justification to conduct another trial; No, no evidence for efficacy and/or worsening with combination treatment; or maybe.
DHEA: Dehydroepiandrosterone; NA: Not applicable.

Table 3. Antipsychotic medication plus adjunctive nonantipsychotic medication in patients with schizophrenia as tested in randomized controlled trials, with an emphasis on persistent symptoms despite antipsychotic treatment (cont.).

Study (year)	Duration (weeks)	n[†]	Combination	Comparator	Useful?[‡]	Ref.
Cholinesterase inhibitors and other agents used in Alzheimer's disease (cont.)						
Akhondzadeh *et al.* (2008)	12	30	Donepezil and risperidone	Risperidone	Yes	[146]
Keefe *et al.* (2008)	12	250	Donepezil and one or more second-generation antipsychotics	One or more second-generation antipsychotics	No	[147]
Schubert *et al.* (2006)	8	16	Galantamine and risperidone	Risperidone	Yes	[148]
Lee *et al.* (2007)	12	24	Galantamine and one or more first-generation antipsychotics	One or more first-generation antipsychotics	Maybe	[149]
Dyer *et al.* (2008)	8	20	Galantamine and one or more antipsychotics	One or more antipsychotics	No	[150]
Conley *et al.* (2009)	12	86	Galantamine and antipsychotic	Antipsychotic	No	[151]
Lindenmayer *et al.* (2011)	52	32	Galantamine and long-acting risperidone injection	Long-acting risperidone injection	No	[152]
de Lucena *et al.* (2009)	12	21	Memantine and clozapine	Clozapine	Yes	[153]
Lieberman *et al.* (2009)	8	138	Memantine and second-generation antipsychotic	Second-generation antipsychotic	No	[154]
Sharma *et al.* (2006)	24	21	Rivastigmine and antipsychotic	Antipsychotic	No	[155]
Chouinard *et al.* (2007)	3 months (total 6 months)	20	Rivastigmine and antipsychotic	Antipsychotic	No	[156]
GABA-A receptor drug						
Lewis *et al.* (2008)	4	15	MK-0777 and one or more antipsychotics	One or more antipsychotics	Yes	[157]
Buchanan *et al.* (2011)	4	60	MK-0777 and one or more second-generation antipsychotics	One or more second-generation antipsychotics	No	[158]
Glutamate receptor agents						
Heresco-Levy *et al.* (1996)	6 (total 14)	11	Glycine and antipsychotic	Antipsychotic	Yes	[159]
Heresco-Levy *et al.* (1999)	6 (total 14)	22	Glycine and antipsychotic	Antipsychotic	Yes	[160]
Potkin *et al.* (1999)	12	19	Glycine and clozapine	Clozapine	No	[161]
Evins *et al.* (2000)	8	30	Glycine and clozapine	Clozapine	No	[162]
Javitt *et al.* (2001)	6 (total 14)	12	Glycine and one or more antipsychotics	One or more antipsychotics	Yes	[163]
Heresco-Levy *et al.* (2004)	6 (total 14)	17	Glycine and olanzapine or risperidone	Olanzapine and risperidone	Yes	[164]
Buchanan *et al.* (2007)	16	157	Glycine or D-cycloserine and antipsychotic	Antipsychotic	No	[165]
Heresco-Levy *et al.* (2005)	6 (total 15)	39	D-serine and risperidone or olanzapine	Risperidone or olanzapine	Yes	[166]
Lane *et al.* (2005)	6	65	D-serine or sarcosine and risperidone	Risperidone	Yes	[167]
Lane *et al.* (2010)	6	60	D-serine or sarcosine and risperidone, olanzapine or quetiapine	Risperidone, olanzapine or quetiapine	Yes	[168]
Lane *et al.* (2006)	6	20	Sarcosine and clozapine	Clozapine	No	[169]
van Berckel *et al.* (1999)	8	26	D-cycloserine and first-generation antipsychotic	First-generation antipsychotic	No	[170]
Heresco-Levy *et al.* (2002)	6 (total 14)	24	D-cycloserine and antipsychotic	Antipsychotic	Yes	[171]
Goff *et al.* (2005)	6 months	55	D-cycloserine and first-generation antipsychotic	First-generation antipsychotic	No	[172]

All studies are double blind and parallel group unless otherwise noted (see **Supplementary Table 3** for further details).
For information on anticonvulsants and lithium see [85].
[†]Randomized.
[‡]Usefulness is summarized by: Yes, there is an efficacy signal for at least some of the important efficacy outcomes for the combination treatment versus the comparator, and can serve as justification to conduct another trial; No, no evidence for efficacy and/or worsening with combination treatment; or maybe.
DHEA: Dehydroepiandrosterone; NA: Not applicable.

Table 3. Antipsychotic medication plus adjunctive nonantipsychotic medication in patients with schizophrenia as tested in randomized controlled trials, with an emphasis on persistent symptoms despite antipsychotic treatment (cont.).

Study (year)	Duration (weeks)	n†	Combination	Comparator	Useful?‡	Ref.
Glutamate receptor agents (cont.)						
Goff *et al.* (2008)	8	38	D-cycloserine (once weekly) and antipsychotic	Antipsychotic	Yes	[173]
Tsai *et al.* (2006)	6	32	D-alanine and one or more antipsychotics	One or more antipsychotics	Yes	[174]
Goff *et al.* (2001)	4	19	CX516 and clozapine	Clozapine	Yes	[175]
Goff *et al.* (2008)	4	105	CX516 and clozapine, olanzapine or risperidone	Clozapine, olanzapine or risperidone	No	[176]
Neurosteroids and hormones						
Kulkarni *et al.* (2001)	4	36	Transdermal estradiol and antipsychotic	Antipsychotic	Yes	[177]
Akhondzadeh *et al.* (2003)	8	32	Ethinyl estradiol and haloperidol	Haloperidol	Yes	[178]
Strous *et al.* (2003); Strous *et al.* (2005)	6	27	DHEA and antipsychotic	Antipsychotic	Yes	[179,180]
Ritsner *et al.* (2006)	12	62	DHEA and one or more antipsychotics	One or more antipsychotics	Yes	[181]
Strous *et al.* (2007)	12	40	DHEA and olanzapine	Olanzapine	Yes	[182]
Ko *et al.* (2008)	4	30	Testosterone gel and antipsychotic	Antipsychotic	Yes	[183]
Kulkarni *et al.* (2008)	4	102	Transdermal estradiol and antipsychotic	Antipsychotic	Yes	[184]
Marx *et al.* (2009)	8	21	Pregnenolone and aripiprazole, olanzapine, quetiapine or risperidone	Aripiprazole, olanzapine, quetiapine or risperidone	Yes	[185]
Kulkarni *et al.* (2010)	12	35	Raloxifene and one or more antipsychotics	One or more antipsychotics	Yes	[186]
Ritsner *et al.* (2010)	8	58	Pregnenolone or DHEA and one or more antipsychotics	One or more antipsychotics	Yes	[187]
Omega-3 fatty acids						
Fenton *et al.* (2001)	16	87	Ethyl-eicosapentaenoic acid and one or more antipsychotics	One or more antipsychotics	No	[188]
Emsley *et al.* (2002)	12	40	Ethyl-eicosapentaenoic acid and antipsychotic	Antipsychotic	Yes	[189]
Opioid system agents						
Rapaport *et al.* (1993)	32–50 days	11	Nalmefene and antipsychotic	Antipsychotic	Yes	[190]
Sernyak *et al.* (1998)	3	21	Naltrexone and antipsychotic	Antipsychotic	No	[191]
Petrakis *et al.* (2004)	12	31	Naltrexone and antipsychotic	Antipsychotic	Yes	[192]
Peptides						
Sheitman *et al.* (2004)	Single dose	22	Intravenous secretin (single dose) and one or more antipsychotics	One or more antipsychotics	Maybe	[193]
Feifel *et al.* (2010)	3	19	Intranasal oxytocin and one or more antipsychotics	One or more antipsychotics	Yes	[194]
Purinergic agents						
Akhondzadeh *et al.* (2000)	8	30	Dipyridamole and haloperidol	Haloperidol	Yes	[195]
Akhondzadeh *et al.* (2005)	8	46	Allopurinol and haloperidol	Haloperidol	Yes	[196]

All studies are double blind and parallel group unless otherwise noted (see **Supplementary Table 3** for further details).
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†Randomized.
‡Usefulness is summarized by: Yes, there is an efficacy signal for at least some of the important efficacy outcomes for the combination treatment versus the comparator, and can serve as justification to conduct another trial; No, no evidence for efficacy and/or worsening with combination treatment; or maybe.
DHEA: Dehydroepiandrosterone; NA: Not applicable.

Table 3. Antipsychotic medication plus adjunctive nonantipsychotic medication in patients with schizophrenia as tested in randomized controlled trials, with an emphasis on persistent symptoms despite antipsychotic treatment (cont.).

Study (year)	Duration (weeks)	n[†]	Combination	Comparator	Useful?[‡]	Ref.
Purinergic agents (cont.)						
Brunstein *et al.* (2005)	6 (total 12)	35	Allopurinol and antipsychotic	Antipsychotic	Yes	[197]
Salimi *et al.* (2008)	8	50	Propentofylline and risperidone	Risperidone	Yes	[198]
Dickerson *et al.* (2009)	8	59	Allopurinol and antipsychotic	Antipsychotic	Yes	[199]
Serotonin 5-HT_{1A} receptor agonists						
Sumiyoshi *et al.* (2001)	6	26	Tandospirone and haloperidol, sulpiride or pimozide	Haloperidol, sulpiride or pimozide	Yes	[200]
Sumiyoshi *et al.* (2007)	6 months	73	Buspirone and risperidone, olanzapine, clozapine or ziprasidone	Risperidone, olanzapine, clozapine or ziprasidone	Yes	[201]
Piskulić *et al.* (2009)	6	18	Buspirone and clozapine, risperidone, olanzapine, quetiapine or amisulpride	Clozapine, risperidone, olanzapine, quetiapine or amisulpride	No	[202]
Ghaleiha *et al.* (2010)	8	43	Buspirone and risperidone	Risperidone	Yes	[203]
Serotonin 5-HT_3 receptor antagonists						
Zhang *et al.* (2006)	12	121	Ondansetron and haloperidol	Haloperidol	Yes	[204]
Akhondzadeh *et al.* (2009)	12	30	Ondansetron and risperidone	Risperidone	Yes	[205]
Wakefulness promoting agents						
Sevy *et al.* (2005)	8	24	Modafinil and one or more antipsychotics	One or more antipsychotics	No	[206]
Pierre *et al.* (2007)	8	20	Modafinil and antipsychotic	Antipsychotic	No	[207]
Freudenreich *et al.* (2009)	8	35	Modafinil and clozapine	Clozapine	No	[208]
Kane *et al.* (2010)	4	60	Armodafinil and risperidone, olanzapine or paliperidone	Risperidone, olanzapine or paliperidone	No	[209]
Others						
Silver *et al.* (2005)	3 (total 6)	29	Amantadine and one or more antipsychotics	One or more antipsychotics	Maybe	[210]
Kaptsan *et al.* (2007)	3 months (total 6 months)	10	Creatine and antipsychotic	Antipsychotic	No	[211]
Akhondzadeh *et al.* (1999)	8	30	Cyproheptadine and haloperidol	Haloperidol	Yes	[212]
Lee *et al.* (1995)	6	40	Cyproheptadine and haloperidol	Haloperidol	No	[213]
Akhondzadeh *et al.* (2002)	8	42	Diazoxide and haloperidol	Haloperidol	Yes	[214]
Levkovitz *et al.* (2010)	22	54	Minocycline and risperidone, olanzapine, quetiapine or clozapine	Risperidone, olanzapine, quetiapine or clozapine	Yes	[215]
Ritsner *et al.* (2011)	8	60	L-theanine and one or more antipsychotics	One or more antipsychotics	Yes	[216]
Berk *et al.* (2008)	24	140	*N*-acetyl cysteine and antipsychotic	Antipsychotic	Yes	[217]
Noorbala *et al.* (1999)	8	30	Piracetam and haloperidol	Haloperidol	Yes	[218]
Ehrenreich *et al.* (2007)	12	39	Recombinant human erythropoietin and antipsychotic	Antipsychotic	Yes	[219]
Strous *et al.* (2009)	8	18	*S*-adenosyl-methionine and one or more antipsychotics	One or more antipsychotics	Yes	[220]
Akhondzadeh *et al.* (2011)	8	40	Sildenafil and risperidone	Risperidone	Yes	[221]

All studies are double blind and parallel group unless otherwise noted (see **Supplementary Table 3** for further details).
For information on anticonvulsants and lithium see [85].
[†]Randomized.
[‡]Usefulness is summarized by: Yes, there is an efficacy signal for at least some of the important efficacy outcomes for the combination treatment versus the comparator, and can serve as justification to conduct another trial; No, no evidence for efficacy and/or worsening with combination treatment; or maybe.
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as some studies focused on patients with ongoing depressive symptoms while others did not. In a meta-analysis [222], outcome was measured as standardized mean difference between end of trial and baseline scores of negative symptoms in 23 trials from 22 publications (n = 819). Included were serotonin-specific reuptake inhibitors, mirtazapine, reboxetine, mianserin, trazodone and ritanserin. The overall standardized mean difference was moderate in favor of antidepressants and subgroup analysis revealed significant responses for fluoxetine, trazodone and ritanserin.

Cognitive dysfunction has also been an active area of research and several potential augmenting medications have been suggested, including agents such as donepezil [137–147], galantamine [148–152], memantine [153,154], rivastigmine [155–156], methylphenidate [131], guanfacine [132], atomoxetine [133,134], modafinil and armodafinil [206–209], with very few encouraging results. Perhaps the greatest promise is with agents that act on glutamate receptors [159–176], although not in combination with clozapine [161,162,169]. Agents that require further study where at least two positive studies have been reported (with no more than two negative studies) include celecoxib [88–91], neurosteroids and hormones [177–187], purinergic agents [195–199], serotonin 5-HT_{1A} receptor agonists [200–203] and serotonin 5-HT_3 receptor antagonists [204,205].

For additional details regarding adjunctive strategies specifically for the domain of aggression [135,136], the reader is referred to prior reviews [9,223].

■ Adjunctive nonpharmacologic interventions

Nonpharmacologic interventions used together with antipsychotic medications include somatic therapies such as transcranial magnetic stimulation and electroconvulsive therapy. Psychological interventions include cognitive behavioral therapy and others. **Table 4 & Supplementary Table 4** outline several randomized controlled trials of these adjunctive nonpharmacological interventions [224–242]. Cognitive-behavioral therapy, although labor-intensive, can be helpful even in patients considered treatment refractory [224–226]. Adjunctive electroconvulsive therapy is another treatment option tested in randomized controlled trials [227,228], and its use with clozapine appears encouraging [243]. Results of individual studies of repetitive transcranial magnetic stimulation (rTMS) in patients with refractory symptoms of schizophrenia have been mixed [229–239]. In a meta-analysis [244], the efficacy of prefrontal rTMS for treating negative symptoms of schizophrenia was assessed in nine trials (n = 213). The overall mean weighted effect size for rTMS versus sham was in the small-to-medium range and statistically significant. Another meta-analysis reported on all prospective studies of rTMS in refractory schizophrenia that assessed the effects of high-frequency rTMS to the left dorsolateral prefrontal cortex for the treatment of negative symptoms, and low-frequency rTMS to the left temporo-parietal cortex for the treatment of auditory hallucinations and overall positive symptoms [245]. The sham-controlled studies did not support the use of rTMS for negative or positive symptoms. However, when specifically examining auditory hallucinations, the effect size for the sham-controlled studies was large and statistically significant [245].

■ Complementary & alternative medicine

When conventional treatments are inadequate, it is not unusual for patients and their families to ask about alternatives (for a review see [246]). An example of complementary and alternative medicine approaches to chronic schizophrenia includes adjunctive use of ginkgo, as reviewed by Singh and colleagues [247]. Six studies were evaluated (n = 828), and ginkgo as an add-on therapy to antipsychotic medication produced statistically significant moderate improvement in total and negative symptoms of chronic schizophrenia. Yi-gan san as adjunctive therapy for treatment-resistant schizophrenia was tested in a 4-week randomized open-label study in 34 patients [248]. A significant decrease was observed at 2 and 4 weeks in each PANSS subscales score in the Yi-gan san group, but this was not observed in the control group. By contrast, a 5-month study of adjunctive megavitamins did not demonstrate any benefits of this approach [249].

Acupuncture for schizophrenia has also been reviewed [250]. A total of 13 randomized controlled trials, all originating from China, were evaluated. One study reported significant effects of electroacupuncture plus drug therapy for improving auditory hallucinations and positive symptom compared with sham electroacupuncture plus drug therapy. Seven studies showed significant effects of acupuncture plus antipsychotic drug therapy for response compared with antipsychotic drug therapy. Two studies tested laser acupuncture against sham

laser acupuncture with one finding beneficial effects of laser acupuncture on hallucinations and the other study showing significant effects of laser acupuncture on response rate, Brief Psychiatric Rating Scale and clinical global index compared with sham laser. It was noted by the authors of the meta-analysis that overall methodological quality was generally poor and that firm conclusions could not be made.

Yoga therapy, when added on to ongoing antipsychotic treatment, yielded advantages over physical exercise therapy in psychopathology outcomes, social and occupational functioning and quality of life as noted in a randomized controlled blinded-rater study [251].

Future perspective

Several new second-generation antipsychotics have received regulatory approval in 2009 and 2010. These include iloperidone, asenapine and lurasidone [252]. However, their basic mechanism of action is similar to that of agents already available and it is unlikely that they will offer efficacy advantages over the current formulary. Their principal advantage appears to be in their metabolically 'friendlier' profile in comparison with some other second-generation antipsychotics. Other antipsychotics in development that exert their action on the dopamine receptor, such as cariprazine [253], are also not expected to provide a paradigm shift.

Table 4. Antipsychotic medication plus nonpharmacological interventions in patients with schizophrenia as tested in randomized controlled trials, with an emphasis on persistent symptoms despite antipsychotic treatment.

Study	Duration	n†	Combination	Comparator	Useful?‡	Ref.
CBT						
Pinto *et al.* (1999)	6 months	41	CBT plus social skills training and clozapine	Supportive therapy and clozapine	Yes	[224]
Valmaggia *et al.* (2005)	22 weeks	62	CBT and antipsychotic	Supportive counseling and antipsychotic	Maybe	[225]
Barretto *et al.* (2009)	21 weeks	21	CBT and clozapine	Befriending and clozapine	Yes	[226]
ECT						
Chanpattana *et al.* (1999)	6 months	51	ECT and flupenthixol	ECT or flupenthixol	Yes	[227]
Goswami *et al.* (2003)	4 weeks	25	ECT and chlorpromazine	Chlorpromazine	Yes	[228]
rTMS						
McIntosh *et al.* (2004)	4 days	16	rTMS and one or more antipsychotics	One or more antipsychotics	No	[229]
Fitzgerald *et al.* (2005)	10 weeks	33	rTMS and second-generation antipsychotic	Second-generation antipsychotic	No	[230]
Lee *et al.* (2005)	10 days	39	rTMS and antipsychotic	Antipsychotic	Yes	[231]
Saba *et al.* (2006)	10 days	18	rTMS and antipsychotic	Antipsychotic	No	[232]
Mogg *et al.* (2007)	10 days	17	rTMS and antipsychotic	Antipsychotic	No	[233]
Prikryl *et al.* (2007)	15 days	22	rTMS and antipsychotic	Antipsychotic	Yes	[234]
Rosa *et al.* (2007)	10 days	11	rTMS and clozapine	Clozapine	No	[235]
Fitzgerald *et al.* (2008)	3 weeks	29	rTMS and antipsychotic	Antipsychotic	Maybe	[236]
Schneider *et al.* (2008)	4 weeks	51	rTMS and second-generation antipsychotic	Second-generation antipsychotic	Yes	[237]
Vercammen *et al.* (2009)	6 days	38	rTMS and antipsychotic	antipsychotic	Yes	[238]
De Jesus *et al.* (2010)	20 days	17	rTMS and clozapine	Clozapine	Yes	[239]
Others						
Jenner *et al.* (2006)	18 months	63	Hallucination-focused integrative treatment and antipsychotic	Antipsychotic	Yes	[240]
Fisher *et al.* (2010)	6 months	32	Targeted cognitive training and medication	Computer games control condition and medication	Yes	[241]
Buchain *et al.* (2003)	6 months	26	Occupational therapy and clozapine	Clozapine	Yes	[242]

See **Supplementary Table 4** for further details.
†Randomized.
‡Usefulness is summarized by: Yes, there is an efficacy signal for at least some of the important efficacy outcomes for the combination treatment versus the comparator, and can serve as justification to conduct another trial; No, no evidence for efficacy and/or worsening with combination treatment; or maybe.
CBT: Cognitive behavioral therapy; ECT: Electroconvulsive therapy; rTMS: Repetitive transcranial magnetic stimulation.

By contrast, drugs that affect glutamate receptors may provide new avenues for the treatment of individuals with schizophrenia who remain with residual cognitive and negative symptoms. Although metabotropic glutamate receptor agonists have been tested as monotherapies in the treatment of schizophrenia [254], ampakines such as CX516 [175,176], kainite receptor drugs such as topiramate [85], and drugs that affect the NMDA receptor [255] are generally used as adjuncts. A glycine transport inhibitor is in commercial development [256]. It is of interest to note that clozapine itself may act as a glycine transport inhibitor [257], perhaps explaining clozapine's uniqueness in terms of its efficacy profile when used as a monotherapy, and that no additional advantage is conferred when it is combined with other drugs that target the NMDA receptor.

Recommendations

Before declaring a patient with schizophrenia as refractory to treatment the clinician should ensure that an adequate trial of medication did take place. This includes consideration of adequate dosing and pharmacokinetic issues such as administration with food if relevant, as seen with ziprasidone [258]. Awareness of potential substance use and/or partial or nonadherence is also critical as these factors can impact treatment response. Consideration of environmental and social obstacles to response also needs to be thought through.

The identification of specific target symptoms must be individualized, and in addition to psychotic symptoms, other symptoms that the patient finds significant are important to make explicit. Other patient-centered concerns are potential tolerability issues that may have interfered with adherence and response in the past. When selecting a potential adjunctive treatment, new tolerability concerns, not discussed here, can complicate expectations and outcomes.

Conclusion

Clozapine remains the standard medication of choice for treatment-refractory schizophrenia. Improvement upon clozapine monotherapy remains elusive to demonstrate in clinical trials. Despite the plethora of randomized controlled trials of putative augmenting agents for treatment-resistant schizophrenia, no single adjunctive agent has been consistently successful in evidencing efficacy in reducing symptoms, improving cognition, or increasing a patient's level of function. Signals for efficacy from small trials have not always been confirmed in larger trials that enroll perhaps a more heterogeneous patient sample. Identifying target symptoms may allow for a rational and pragmatic choice among all the adjunctive strategies presented in this article (for example an antidepressant where negative or depressive symptoms are present), and thus the clinician may want to systematically conduct an 'n-of-1' trial for a specific individual, being mindful of tolerability and safety issues, in the hopes of achieving a successful outcome.

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