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Review

Pharmacological approaches to treating negative symptoms: A review of clinical trials

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ABSTRACT

Clinical trials of pharmacological agents targeting negative symptoms in schizophrenia are reviewed. The focus is on trials that occurred in patients who were stable on an antipsychotic medication at entry to the trial. A small number of trials compared antipsychotics as monotherapy for negative symptoms. Although the data supporting amisulpride for negative symptoms is promising the trials have limitations and it is plausible that the advantages of amisulpride over placebo may result from effects on secondary negative symptoms. Among available agents, antidepressant medications may have effects in negative symptoms. Other promising agents include minocycline, glutamatergic agents, and alpha-7 nicotinic agents. More than 15 active trials are currently underway to evaluate new treatments for negative symptoms.

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1. Introduction

Negative symptoms are an important target for drug development for a number of reasons: (1) negative symptoms are relatively common with a recent study finding that nearly 58% of outpatients had at least one negative symptom (Bobes et al., 2010); (2) negative symptoms are better predictors of functioning than positive symptoms (Rabinowitz et al., 2012); and (3) there are no accepted treatments for primary negative symptoms. With the possible exception of amisulpride in some countries, antipsychotic medications are relatively ineffective for managing negative symptoms in stable patients. This lack of effectiveness is not surprising since complex disorders such as schizophrenia may include families of related disorders. In schizophrenia, patients may have impairments in a number of psychopathological domains including psychotic symptoms, cognitive impairments, and negative symptoms. As a result, it may be unrealistic to expect a single drug to treat all aspects of the disorder (Hyman and Fenton, 2003; Arango et al., 2004; Carpenter and Davis, 2012). Recent attention has focused on the development of pharmacological agents that have specific activity in treating negative symptoms that can be added to an antipsychotic medication (Arango et al., 2004; Kirkpatrick et al., 2006; Marder et al., 2011).

This review will focus on clinical trials of pharmacological agents for treating negative symptoms. We have selected trials that used specific entry criteria for negative symptoms and excluded trials that measured negative symptom change in individuals with acute psychosis. In most cases, the trials fit recent guidelines for negative symptom trials (Marder et al., 2011). That is, negative symptoms were stable and persistent. In addition, other causes of negative symptoms such as depression, extrapyramidal side effects, and psychosis were not sufficiently severe to cause secondary negative symptoms. Studies used different criteria for assuring that persistent positive symptoms such as hallucinations and delusions were not causing negative symptoms such as emotional withdrawal and avolition. These varied from studies requiring that positive symptoms be no greater than mild to studies that permitted moderately severe positive symptoms. This review includes three sections: (1) trials of drugs that are approved for schizophrenia and other illnesses and have also been evaluated for negative symptoms; (2) newer drugs that are not approved and have been evaluated for negative symptoms; and (3) trials of agents for negative symptoms that are currently underway or that have not published results.

2. Studies with approved agents

This review includes published trials evaluating approved agents in negative symptoms of schizophrenia from 1995 to 2012. Our search found multiple published studies and meta-analyses evaluating monotherapy antipsychotics in patients with prominent or predominant negative symptoms. Most of these studies focused on negative symptom improvement in patients with acute schizophrenia and were not included. As a result, this review is limited to studies of clozapine, amisulpride and asenapine.

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2.1. Clozapine

Early comparisons of clozapine with other antipsychotics in treatment resistant and acutely ill patients suggested that clozapine may be more effective for treating negative symptoms (Kane et al., 1988). Although clozapine may have been more effective when compared with haloperidol and other antipsychotics with substantial EPS liabilities, this advantage is not apparent with lower EPS agents (Essali et al., 2009). In addition, studies of a longer duration have failed to find advantages of clozapine for negative symptoms. For example, a VA Cooperative Study (Rosenheck et al., 1999) evaluated patients over a one year period and did not find that clozapine had independent effects on negative symptoms. A 29 week comparison of clozapine and haloperidol also failed to find an advantage for clozapine on negative symptoms (Kane et al., 2001).

One study (Breier et al., 1994) evaluated the effects of clozapine on negative symptoms in deficit and non-deficit patients. Deficit patients were those who demonstrated primary rather than secondary negative symptoms. Clozapine was only effective for treating negative symptoms in the non-deficit patients. Taken together, studies of clozapine suggest that it has advantages for negative symptoms that may be secondary to extrapyramidal side effects or inadequately treated positive symptoms. It does not appear to be effective for primary negative symptoms.

2.2. Amisulpride

Amisulpride, a substituted benzamide, is a selective dopamine D2 antagonist approved in multiple European countries for the treatment of positive and negative symptoms of schizophrenia. Four studies (Loo et al., 1997; Danion et al., 1999; Moller, 2001) evaluated amisulpride monotherapy compared with placebo in patients with predominant negative symptoms of schizophrenia. Patients were selected based on their high scores of the Scale for the Assessment of Negative Symptoms (SANS), low scores of the Scale for the Assessment of Positive Symptoms (SAPS) and extrapyramidal (EPS) scores. All studies used the SANS as the primary outcome parameter. Study duration varied from 6 to 26 weeks. The dose of amisulpride ranged from 50 to 300 mg.

All studies showed a significant improvement on negative symptoms compared with placebo. This improvement on negative symptoms was not accompanied by an improvement on positive symptoms in 3 out of 4 studies. In the fourth study (Danion et al., 1999), both negative and positive symptoms improved significantly compared with placebo. In all studies, placebo-treated patients improved significantly on negative symptoms compared with their baseline severity.

One study (Lecrubier et al., 2006) evaluated two doses of olanzapine (5 and 20 mg), 150 mg of amisulpride, and placebo in 244 patients with predominant negative symptoms. The 5 mg olanzapine group showed greater improvement than placebo in negative symptoms, but not the amisulpride groups. Two additional studies (Speller et al., 1997; Moller, 2000), with at least 25 patients per treatment arm, compared the efficacy of amisulpride with low doses antipsychotics (haloperidol and fluphenazine) for negative symptoms. Neither studies showed a superior efficacy of amisulpride.

2.3. Asenapine

Asenapine is approved for the treatment of schizophrenia in most countries. Trials in patients with acute exacerbations suggested that asenapine was more effective than risperidone and haloperidol for negative symptoms (Potkin et al., 2007; Kane et al., 2010a). Two randomized double-blind studies (Buchanan et al., 2012) compared the effect of asenapine with olanzapine in stable patients with predominant negative symptoms of schizophrenia. Predominant negative symptoms were defined as a PANSS (Positive and Negative Scale (Kay et al., 1987)) negative symptom subscale total of 20 or greater and a score of 4 on 3 or more of the 7 Marder Negative Symptom Factor Scores (Marder et al., 1997). Patients with a score of 4 or greater on more than 2 items of the positive subscale of the PANSS were excluded. Patients needed to be stable for at least 5 months before screening, and have a low score on the Calgary Depression Scale of Schizophrenia (CDSS) and the abbreviated Extrapyramidal Symptoms Rating Scale (ESRS-A). Patients were excluded if they were treated with olanzapine within 5 months prior to screening and failed to benefit on negative symptoms. The prospectively defined primary efficacy variable was the change on the 16-item Negative Symptoms Scale (NSA-16(Axelrod et al., 1993)) total at Study Week 26. Both test drugs, asenapine and olanzapine, were associated with a significant improvement on persistent negative symptoms compared with baseline. There was no significant difference between asenapine and olanzapine on the total NSA score, the primary outcome parameter.

3. Studies evaluating adjunctive therapy with available medications for the treatment of negative symptoms of schizophrenia

3.1. Antidepressant drugs

A meta-analysis (Singh et al., 2010) evaluated the efficacy of antidepressant adjunctive to antipsychotic therapy. Although there were many case reports and open label trials where antidepressants were added to an antipsychotic, only trials that used well-described criteria for negative symptoms and used double-blind methods to compare the antidepressant to a placebo were included. This resulted in the inclusion of 23 trials from 22 publications (n = 819 patients). In most studies, mean scores of negative symptoms were equally or more severe than those of positive symptoms. Study durations varied from 4 to 12 weeks. However, it is unclear whether patients' with depression or severe depressive symptoms were excluded. The overall standardized mean difference was modest (ES-0.33) in favor of antidepressants. Subgroup analyses revealed significant responses for fluoxetine, trazodone and ritanserin. The results supported some benefit of antidepressants in patients with prominent negative symptoms.

3.2. Minocycline

Minocycline is a tetracycline antibiotic with emerging interest for its neuroprotective properties against glutamate neurotoxicity in cell culture and in rodent models of neurodegenerative disorders. Two studies evaluated the effect of minocycline 200 mg/day in early schizophrenia for negative symptoms.

Levkovitz et al. (2010) reported results from a study evaluating the effects of minocycline. Subjects aged 18 to 35 years, within 5 years from their first episode, not receiving antipsychotic treatment for at least 6 months prior to the current episode, and the antipsychotic treatment was initiated less than 14 days prior to the study. A total of 54 patients with PANSS greater than 60 at baseline were randomized to receive minocycline (36) or placebo (18) adjunctive to atypical antipsychotic therapy. Patients treated with minocycline showed greater improvement in negative symptoms measured by the SANS than placebo patients.

Chaudhry et al. (2012) reported results from a study conducted in Brazil and Pakistan. Subjects were aged 18 to 65 years, within 5 years of diagnosis, stable on medication for 4 weeks prior to baseline. A total of 144 participating patients were randomized to receive minocycline (71) or placebo (73) adjunctive to antipsychotic treatment. Data from both participating countries are presented separately, thus making it difficult to extrapolate the overall results. However, the authors concluded that the addition of minocycline to treatment as usual early in the course of schizophrenia improves negative symptoms.

3.3. Dopamine agonists

Dopamine antagonism can produce negative symptoms in healthy volunteers and in animal models (Wise et al., 1978; Artaloytia et al., 2006). For that reason, dopamine agonists may play a role in the treatment of negative symptoms, although the evidence is mixed. Selegiline, a monoamine oxidase-B inhibitor that selectively enhances dopaminergic activity, has been shown to reduce negative symptoms of schizophrenia in open-label studies (Bodkin et al., 1996), and in double-blind, placebo-controlled studies (Bodkin et al., 2005; Amiri et al., 2008), although there are also negative findings (Jungerman et al., 1999).

Lisdexamfetamine, a D-amphetamine pro-drug was evaluated in a 10 week open label study of patients who were stabilized on an antipsychotic (Lasser et al., 2013). Lisdexamfetamine was effective for reducing negative symptoms on the PANSS. This finding clearly needs to be evaluated in a double-blind study.

Modafinil, a stimulant that modestly inhibits dopamine and norepinephrine transporters, leading to increased dopamine and norepinephrine efflux in cortical and other brain areas, has been found to improve negative symptoms in an 8-week double-blind trial when added to risperidone (Arbabi et al., 2012). Two trials evaluated a mixed group of patients with fatigue and negative symptoms where modafinil was added to typical and atypical antipsychotics (Sevy et al., 2005) or clozapine (Freudenreich et al., 2009). Neither trial found an effect on negative symptoms when compared to placebo.

There are also mixed results for the modafinil R-enantiomer armodafinil. A proof of concept trial showed that one of three doses used (200 mg/day) in a 4-week, double-blind, placebo-controlled study with 60 stable schizophrenia patients significantly reduced negative symptoms (Kane et al., 2010b). It is noteworthy that beneficial effects were found on the PANSS but not the SANS and negative symptoms were not required for study subjects. A later larger study with 285 stable schizophrenia patients with negative symptoms was unable to replicate the findings, with no difference among three different armodafinil doses (150 mg, 200 mg, or 250 mg) and placebo in a 24-week trial (Kane et al., 2012).

3.4. Cholinergic agents

Acetylcholinesterase inhibitors increase the synaptic levels of acetylcholine leading to increased stimulation of nicotinic, and muscarinic receptors. These drugs have been found to be effective for treating the cognitive symptoms of dementia and a number are approved for this indication. The effects of acetylcholinesterase inhibitors have been tested in patients with schizophrenia and cognitive impairment. In addition, a number of studies have also assessed their effects on negative symptoms. A Cochrane meta-analysis of the few studies published until 2009 suggests a benefit of an acetylcholinesterase inhibitor plus antipsychotic over antipsychotic and placebo on PANSS negative symptoms (average endpoint score (2 RCTs, n = 31, MD −1.69 95% CI −2.80 to −0.57)) (Singh et al., 2012). The authors mention that the many limitations of the studies included in the analysis make this weak evidence and stress the need for more well-designed, large, randomized studies.

In a 12-week, double-blind, placebo-controlled trial with 86 stable patients treated with antipsychotics, galantamine (an acetylcholinesterase inhibitor and a positive allosteric modulator at nicotinic receptors) was found to improve alogia, although there were no significant changes in global negative symptom scores (Conley et al., 2009). In another study with a very similar design, 30 stable schizophrenia patients on risperidone (4–6 mg/day) received donepezil or placebo (Akhondzadeh et al., 2008). Although there was no change in cognitive performance, donepezil-treated patients experienced an improvement in negative symptoms. This effect was not seen in 20 elderly chronic patients (mean age 70.2) in another study comparing donepezil with placebo. The latter was a 12-week, double-blind, add-on, crossover clinical trial (Mazeh et al., 2006).

4. New pharmacological agents

4.1. Cholinergic

A partial alpha7 nicotinic receptor agonist, 3-(2,4-dimethoxybenzylidene) anabaseine (DMXB-A) was shown to improve negative symptoms as measured by the SANS in 31 stable schizophrenia patients in a double-blind, crossover, add-on study (Freedman et al., 2008). It is interesting to note that the authors developed this study to target cognitive impairment, but found more consistent effects on negative symptoms. Lieberman et al. (2013) recently reported that a partial alpha7 nicotinic receptor agonist, TC-5619, led to significant improvement in negative symptoms in a 12-week, double-blind, placebo-controlled, add-on study of 185 schizophrenia patients treated with quetiapine or risperidone monotherapy. This agent is currently being evaluated in a phase 3 trial for negative symptoms (as noted in the next section on trials in progress).

4.2. Glutamate

The “NMDA receptor hypofunction hypothesis” of schizophrenia was first documented in the 1980s (Coyle, 2012). The connection between the NMDAR and schizophrenia was based on the recognition that ketamine and phencyclidine (PCP), non-competitive antagonists of the NMDAR, had psychotomimetic effects and induce schizophrenia-like psychosis, including not only positive but also negative symptoms (Domino et al., 2004; Coyle, 2012). There is also convergent evidence that involves NMDAR-related gene expression and metabolic pathways in schizophrenia (Moghaddam and Javitt, 2012).

A number of novel pre- and postsynaptic mechanisms affecting glutamatergic synaptic transmission have emerged as viable targets for the treatment of negative symptoms in schizophrenia (Javitt, 2012). Several classes of drugs with different mechanisms of action involving the glutamatergic system have achieved promising results. Most of these drugs are metabotropic glutamate agonists, glycine transport inhibitors, drugs that act at the glycine/D-serine and redox sites of the NMDAR and pathways regulating glutamate, glycine/D-serine and glutathione synthesis/release (Javitt, 2012).

4.2.1. NMDAR glycine-site agonists

Initial studies with high doses of glycine as an add-on medication report efficacy for the treatment of negative symptoms in three small 6-week, placebo-controlled, add-on studies (Javitt et al., 1994; Heresco-Levy et al., 1996; Heresco-Levy et al., 2004). Glycine has not been shown to be efficacious when added to clozapine (Potkin et al., 1999; Evins et al., 2000). There have also been positive results for D-cycloserine. In a dose-finding study, Goff et al. (1995) found an inverted-U dose-response curve, with maximum therapeutic efficacy at 50 mg/day and loss of efficacy with doses below 50 mg/day or above 100 mg/day. Positive results have been observed in a group of 23 deficit syndrome patients treated with conventional antipsychotics (Goff et al., 1999) and inpatients who received D-cycloserine (50 mg once weekly) and who were treated with antipsychotics other than clozapine (Goff et al., 2008). On the contrary, D-cycloserine seems to worsen negative symptoms when added to clozapine (Goff et al., 1996; Goff et al., 1999) or has no effect when used at doses other than 50 mg/day (Cascella et al., 1994; Rosse et al., 1996; Duncan et al., 2004). There have also been negative results with D-cycloserine used at a dose of 50 mg/day in a 6-month trial (Goff et al., 2005). D-alanine, another endogenous agonist of the NMDA-glycine site, has also been shown to improve negative symptoms in a 6-week, double-blind, placebo-controlled, add-on trial (Tsai et al., 2006).

D-serine was shown to have a beneficial effect in a 6-week, double-blind, placebo-controlled add-on trial (Tsai et al., 1998) but no effect when the same dose (30 mg/kg per day) was added to clozapine in a very similar study (Tsai et al., 1999). In a subsequent study, D-serine was superior to placebo at high doses (50 mg/day) in a 6-week, placebo-controlled, crossover trial in 11 schizophrenia patients treated with clozapine (Goff et al., 2001) and in an open-label study in 42 antipsychotic-stabilized patients at doses of 30, 60, or 120 mg/kg/day (Kantrowitz et al., 2010).

However, the two largest multicenter studies did not replicate the previous findings and no significant effect on negative symptoms was observed as compared with placebo. Buchanan et al. (2007) conducted a 16-week study (n = 157) in which neither glycine (60 mg/day) nor D-cycloserine as add-on drugs improved negative symptoms. The second multicenter study (n = 195) also did not find a positive effect for add-on D-cycloserine (2 g/day) in a 16-week study (Weiser et al., 2012).

4.2.2. Glycine transport inhibitors

Bitopertin (RG1678, Roche), a glycine transport inhibitor was found to induce beneficial effects on negative symptoms in a phase II study. Doses of 10 and 30 mg/day significantly differ from placebo in an 8-week clinical trial (Umbricht et al., 2012). There are three ongoing phase III studies with Bitopertin to assess its efficacy on negative symptoms. In a study comparing the efficacy of D-serine and sarcosine, a glycine transporter-1 (GlyT-1) antagonist, in a 6-week, double-blind, placebo-controlled, add-on trial, sarcosine treatment was better than D-serine in effect sizes for all outcome measures including negative symptoms (Lane et al., 2010).

4.3.3. Metabotropic receptors

Pomaglumetad (LY404039), a highly selective agonist for metabotropic glutamate receptor 2 (mGlu2) and metabotropic glutamate receptor 3 (mGlu3), showed efficacy for the treatment of negative symptoms in a phase II placebo-controlled clinical trial in acute schizophrenia (Patil et al., 2007). Subsequently, four pomaglumetad doses (10, 40, 80, and 160 mg/day) failed to separate from placebo in a failed trial with olanzapine as active comparator (Kinon et al., 2011) (Kinon et al., 2011). More recently a subsequent trial of pomaglumetad indicated that the drug did not separate from placebo (Hopkins, 2013).

There are also some promising results with N-Acetylcysteine (NAC), an activator of the metabotropic receptor mGluR2/3 and the precursor of cysteine, and an indirect antioxidant as a rate-limiting factor in the synthesis of glutathione (GSH). NAC was found to improve core symptoms of schizophrenia, including negative symptoms, as an add-on treatment in a double-blind controlled trial (Berk et al., 2008).

Pregnenolone, a neurosteroid that may exert its effects through positive modulation of NMDA receptors, has been shown to improve negative symptoms as compared with placebo in a small (n = 21) 8-week, double-blind trial in stable patients receiving atypical antipsychotics (Marx et al., 2009) However, a later larger study could not replicate this finding (Ritsner et al., 2010). Two double-blind, placebo-controlled, add-on studies have demonstrated that dehydroepiandrosterone (DHEA) improves negative symptoms at doses between 100 and 150 mg/day (Strous et al., 2003; Strous et al., 2007). However, there are also two negative studies with DHEA (Ritsner et al., 2006; Ritsner et al., 2010).

5. Other approaches

There are a number of other treatment strategies that have been tried in proof of concept studies. Adjunctive intranasal oxytocin for 3 weeks was determined to not be better than placebo for negative symptoms in a small group of 28 subjects (Lee et al., 2013). Ginkgo biloba has also been shown to reduce negative symptoms as compared with placebo in haloperidol treated patients with schizophrenia (Zhang et al., 2001) (Zhang et al., 2001). Recently, 2 mg of folic acid and 400 μg of vitamin B12 showed efficacy for negative symptoms in a 16-week, randomized, double-blind, placebo-controlled clinical trial when genotype was taken into account (Roffman et al., 2013).

Serotonin 5HT3 receptor antagonists including ondansetron, granisetrone, and tropisetrone have also been studied for negative symptoms. Ondansetron was evaluated in two studies as an adjunctive treatment. Both found statistically significant improvements in negative symptoms (Bennett and Vila, 2010). Granisetron and tropisetron were evaluated in separate trials as an adjunctive agent to risperidone. Both studies found improvement in negative symptoms (Khodaie-Ardakani et al., 2013; Noroozian et al., 2013). Tropisetron – which is also an agonist at alpha 7 nicotinic receptors – was also found to improve cognition (Shiina et al., 2010). These trials are certainly interesting, but each has a very modest sample size.

6. Trials that have not reported results

We used the www.clinicaltrials.gov site to document trials that are still recruiting or have not reported results. Trials were located using the search terms negative symptoms and schizophrenia. The table lists the trials along with the proposed mechanism, trial duration, and the instrument used to measure negative symptoms. We only included studies that specified improvement on a negative symptom scale as a primary outcome measure.

Agent	Sponsor	Mechanism	Phase	Age	Duration (wks)	Neg symptom instrument
New agents						
TC5619	Targacept	Partial agonist α7 nicotinic receptor	2	18–60	24	SANS
RO4917838 (Bitopertin)	Hoffmann-La Roche	GlyT1 inhibitor	3	>18	24 w/ extension	PANSS neg factor
AMG 747	Amgen	GlyT1 inhibitor	2	18–60	12	NSA-16
AZD8529 (completed)	Astra Zeneca	mGlu2/3 receptor PAM			4	
ORG 25935 (completed)	Schering-Plough	GlyT1 inhibitor	2	18–55	12	SANS
D-serine	Sheba Medical Center	NMDA co-agonist	2	18–65	16	SANS
	Yale			18–65	12	SANS
LY2140023 (completed)	Lilly	mGlu2/3 agonist	2	18–65	17	NSA-16
New indications						
Lisdexamfetamine	Shire	Dextroamphetamine prodrug	3	18–65	12	NSA-16

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Agent	Sponsor	Mechanism	Phase	Age	Duration (wks)	Neg symptom instrument
Rasagiline	U of Maryland	MAO type B inhibitor	4	18–64	12	SANS
Oxytocin	U of Maryland		2	18–64	8	SANS
Galantamine	U of Maryland	Cholinesterase inhibitor, allosteric nicotinic modulator	2	18–64	8	SANS
Citalopram	Imperial College London	SSRI	4	18–75	52	Heinrich's Quality of Life Scale
Pregnenolone	Veterans Affairs and Cornell	Neuroactive steroid	2	21–65	8	SANS
Citalopram and reboxetine	Sant Joan de Deu and CIBERSAM (Spain)	SSRI and NRI	4	18–65	24	PANSS negative
Levodopa/carbidopa	Centre for Addiction and Mental Health — Toronto	Dopamine	2	18–55	8	SANS
Devices						
Intermittent theta burst	Hôpital le Vinatier (France)			18–50	12	SANS
Deep transcranial magnetic stimulation	Shalvata Mental Health Center			18–65	8	SANS
Transcranial direct current stimulation	University of Sao Paulo		2	18–59	4	PANSS

The table demonstrates that negative symptoms in schizophrenia are a very active area for treatment discovery. There are a number of interesting patterns. The most common mechanisms being studied for new entities are alpha 7 nicotinic and glutamatergic. A review of trials for cognition in schizophrenia shows that this is also a very common target. Studies of cognition using these mechanisms commonly have negative symptoms as a secondary outcome measure. These trials are not included in this table. Among studies using devices, there are a number of promising approaches. As would be expected, trials of newer agents are almost always industry sponsored, whereas studies of approved compounds for a new indication are mostly coming from academic sites.

Although the SANS remains the most common scale for measuring negative symptoms, a number of recently initiated studies are utilizing the NSA-16 and PANSS factor scores. Most of the larger industry trials are 12 to 24 weeks. The relative merits of the different measures are discussed in Marder et al. in this issue.

7. Discussion

This review indicates that clinicians who are treating negative symptoms in schizophrenia have a number of current options for treating negative symptoms in schizophrenia. These options include selecting amisulpride as an antipsychotic (where it is available), or adding one of a number of adjunctive or co-medications to an antipsychotic. Among promising adjunctive medications, there is some modest evidence suggesting that adding an antidepressant may have some benefit. The evidence for other co-medications such as minocycline, modafinil, armodafinil, and galantamine is more limited. A number of promising drugs are currently in different stages of development and it is possible that in the near future more effective adjunctive drugs will be available. At this time, drugs that act at the NMDA and alpha 7 nicotinic receptors are receiving the most attention.

The studies evaluating antipsychotic monotherapy treatment have some methodological limitations. The most serious issue is the ability to demonstrate a direct effect on negative symptoms that is not mediated through alleviation of positive, mood symptoms or antipsychotic-induced motor effects. Studies to evaluate the effect of amisulpride on negative symptoms recruited patients with predominant negative symptoms and minimal positive and mood symptoms. The direct effect observed with amisulpride on primary negative symptoms is the most convincing. However, the impact of this improvement on patient functioning was not investigated. In addition, the study population that received placebo was not receiving an antipsychotic. As a result, the improvement in negative symptoms on amisulpride could have resulted from improvement in low level positive symptoms.

Studies evaluating the effect of therapies adjunctive to antipsychotics also have important limitations. First, these studies enrolled very heterogeneous patient populations using different criteria for persistent negative symptoms. Although some antidepressants have shown an effect on negative symptoms, it is unclear whether this is a direct effect on negative symptoms or if it is mediated through an improvement of mood symptoms. Finally, the effect of minocycline on negative symptoms early in the disease is inconclusive, and clearly needs to be replicated in larger trials.

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Contributors

Drs. Marder, Arango, and Garibaldi each contributed to the literature review and the conclusions in this article.

Conflict of interests

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