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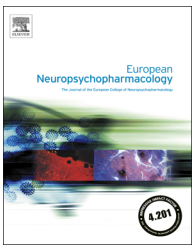

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Psychopharmacology of the negative symptoms: Current status and prospects for progress

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Abstract
The past decade has witnessed a resurgence of interest in the development of novel pharmacological agents to treat the negative symptoms of schizophrenia. This review provides an overview of pharmacological approaches that have been evaluated as potential treatments and describes the emergence of several promising new approaches. First, we briefly describe recent methodological developments, including consensus-based clinical trial guidelines for patient selection criteria, symptom assessment, and trial duration. Next, we overview mono- and adjunctive-therapies that have been evaluated, including first- and second-generation antipsychotics, antidepressants, psychostimulants, molecules targeting cholinergic and glutamatergic systems, and hormones. We highlight the most promising pharmacological agents on the horizon, including glycine transporter-1 inhibitors, α7-nicotinic receptor positive allosteric modulators, and oxytocin, as well as non-pharmacological electromagnetic stimulation approaches. Further investigations, using optimal clinical trial design, hold considerable promise for discovering effective treatments for these functionally disabling symptoms in the near future.
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1. Introduction

Negative symptoms of schizophrenia—blunted affect, alogia, anhedonia, asociality, and avolition—are substantially more resistant to current pharmacological treatments than are positive symptoms (Erhart et al., 2006). There are currently no pharmacological agents with a labeling indication for the treatment of negative symptoms, with the exception of amisulpride in some countries (such as the United Kingdom and Australia). The significant correlation of negative symptoms with poor functional and long-term outcomes (Ventura et al., 2009), however, emphasizes the importance of developing more effective treatments.

In the past decade, through the combined efforts of government, the pharmaceutical industry, and academia (Hughes, 2009; Kirkpatrick et al., 2006; Marder et al., 2011), there has

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been a resurgence of interest in the development of novel pharmacological agents to treat negative symptoms. This has fostered important advances in assessment, clinical trial methodology, and novel pharmacological agents that will hopefully make effective treatments for negative symptoms a reality in the near future.

This descriptive review article provides a general overview of pharmacological treatments for negative symptoms. We first describe key methodological issues that are currently widely regarded as important for designing and interpreting clinical trials for negative symptoms. We then overview various mono- and adjunctive-pharmacological approaches that have been evaluated for the treatment of negative symptoms, with the caveat that many early trials treated negative symptoms as a secondary outcome rather than the primary focus of the study. We then highlight several pharmacologic mechanisms as well as specific drug and other somatic treatments that are being actively investigated for the treatment of negative symptoms. Given the breadth of this topic, we encourage the reader to refer to reviews and original studies referenced in the text for detail.

2. Methodological considerations

Historically, a number of methodological issues have limited the interpretability of research into pharmacological treatments for negative symptoms. Clinical trials have varied considerably in terms of how negative symptoms are defined and measured, whether potential secondary sources of negative symptoms were considered, and the duration of trials. For example, commonly used clinical assessment tools such as the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982; Levine and Leucht, 2013), and Negative Symptom Assessment (NSA-16) (Axelrod et al., 1993) are based on different conceptualizations and coverage of the negative symptom domain (Blanchard et al., 2011). In addition, studies have often not considered possible secondary sources of negative symptoms. Primary negative symptoms, also sometimes referred to as deficit symptoms (Carpenter et al., 1985), are generally considered enduring and intrinsic to schizophrenia whereas secondary negative symptoms are attributable to another underlying cause, such as depression, extrapyramidal symptoms (EPS), or positive psychotic symptoms. Finally, trial durations have ranged widely, from 4 weeks up to 2 years (Marder et al., 2011). These major methodological differences have made it difficult to evaluate whether pharmacological treatments have specific benefits for primary negative symptoms and have impeded progress in treatment development.

The renewed research attention on negative symptoms has helped the field clarify several key methodological factors that need to be considered in designing and interpreting clinical trials. There appears to be widespread consensus on several issues concerning assessment, sample characteristics, and trial design, including the following (Kirkpatrick et al., 2006; Marder et al., 2011):

(1) Definition of negative symptoms: consensus-based definitions of negative symptoms currently include the following five sub-domains: blunted affect, alogia, anhedonia, asociality, and avolition.
(2) Assessment: negative symptoms should be assessed with a validated interview-based measure.
(3) Negative symptoms should be stable and persistent: this may be operationally defined using criteria for persistent negative symptoms (Buchanan, 2007) or the deficit form of schizophrenia (Carpenter et al., 1988). Only stable outpatients should be enrolled in negative symptoms trials.
(4) Secondary negative symptoms: symptoms in other domains, particularly psychotic symptoms, depression, extrapyramidal symptoms, and cognitive impairment, should be stable and not predominant. This will help to ensure that negative symptom change during the course of the trial is not secondary to change in other domains. For example, studies that find improvement in negative symptoms during studies in acutely psychotic schizophrenia patients can be difficult to interpret because improvement in symptoms such as suspiciousness can lead to improvement in secondary negative symptoms.
(5) Trial duration: clinical trials evaluating treatments for negative symptoms should be of longer duration than those targeting positive symptoms. The extra time is necessary because negative symptoms do not improve at the same rate as do positive symptoms (Levine and Leucht, 2012). Preregistration trials should be at least 6 months in duration, not including prospective assessment of clinical stability. A briefer duration of treatment is acceptable for proof-of-concept trials.
(6) Adjunctive agents in clinical trials: In trials addressing the use of co-medications to treat negative symptoms, all antipsychotics, including the simultaneous use of >1 antipsychotic, may be allowed except when the antipsychotic has a potential pharmacokinetic or pharmacodynamic interaction with the experimental medication.
(7) Monotherapy trials: an experimental medication being considered for broad spectrum antipsychotic efficacy (e.g., improving both positive and negative symptoms) should initially be demonstrated as effective in treating positive symptoms. It can then be tested in a comparator trial against another antipsychotic that does not have effects on negative symptoms, while carefully assessing potential confounders (e.g., depression, EPS, etc.) to show improvements are specific for primary negative symptoms.

The United States Food and Drug Administration (FDA) has endorsed negative symptoms of schizophrenia as a legitimate drug target for a labeling indication and has offered guidelines for development (Laughren and Levin, 2011). The European Medicines Agency has similarly offered guidelines for claiming effects on negative symptoms, which convey similar principles as the points listed above. As described in the following sections, incorporating these methodological and design guidelines has been a relatively recent development in the history of clinical trials that consider negative symptoms.

3. Pharmacological approaches

Many classes of medications have been examined as potential treatments for negative symptoms of schizophrenia over