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Clinical management of negative symptoms of schizophrenia: An update



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ABSTRACT

Overwhelming research evidence suggests that the negative symptoms of schizophrenia (NSS) contribute more to impaired quality of life and poor functioning than positive symptoms, and that NSS, including affective flattening, avolition and anhedonia are present in at least one-fifth of patients diagnosed with schizophrenia. Despite this, management of NSS continues to be a major clinical unmet need as treatment with current antipsychotic medication seems to reach at best modest efficacy.

A critical review of the current pharmacological, non-pharmacological and psychosocial treatments available for NSS is presented here, using data retrieved from the MEDLINE/PUBMED, the Cochrane Database of Systematic Reviews and the ClinicalTrials.gov databases. An early and accurate diagnosis using selective scales is essential for documentation and monitoring of change in NSS according to treatment response. Typical and atypical antipsychotic drugs, showed modest efficacy in managing NSS. Conflicting results were obtained with the use of glycinergic neuromodulators, anticholinergics, antidepressants, anticonvulsants, psychostimulants, modafinil and 5-HT₃ receptor antagonists. Moreover, non-pharmacological therapies including psychological therapies have failed to address NSS effectively.

At present, it appears that the best effective approach for clinical management of NSS is achieved by complementing drug therapy with psychosocial therapies. Continuing basic and clinical research for the understanding of the genetic, behavioral and neural basis of NSS should yield novel pharmacotherapies with superior efficacy, tolerability and long-term maintenance for improved treatment of NSS.

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Abbreviations: BNSS, brief negative symptom scale; BPRS, brief psychiatric rating scale; CAINS, clinical assessment interview for negative symptoms; CATIE, clinical antipsychotic trials of intervention effectiveness; CBT, cognitive behavioral therapy; CGI, clinical global impression; COX-2, cyclooxygenase-2; DA, dopamine; ECT, electroconvulsive therapy; NAC, N-acetylcysteine; NSA-16, negative symptom assessment; NSS, negative symptoms of schizophrenia; PANSS, positive and negative syndrome scale; rTMS, repetitive transcranial magnetic stimulation; SANS, scale for the assessment of negative symptoms; 5-HT, serotonin.

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1. Introduction

Schizophrenia is a serious neuropsychiatric disorder that involves major disruption of thinking, perception, emotions and behavior in patients, associated with substantial morbidity, disability, and potential mortality. It carries substantial socioeconomic burden on patients, caregivers, and healthcare providers. The symptoms of the disorder, which starts in late adolescence or early adulthood, fall into three broad categories: positive symptoms including hallucinations, delusions and thought disorders; negative symptoms including affective flattening, social withdrawal and neglect of hygiene; and cognitive impairments including deficits in attention, executive functioning and working memory (Kandel et al., 2000; Nasrallah & Weinberger, 1986; Baldessarini, 1977). Injuries during the normal development of human brain including maldevelopment of the organization and connectivity of cortical afferents innervating the limbic regions (Weinberger, 1987), and altered interactions between dopamine (DA) and serotonin (5-HT) systems, in different cortical, limbic and extrapyramidal pathways (Meltzer, 1989; Baldessarini & Tarazi, 2005) may provide neurobiological substrates for the development of schizophrenia.

Overwhelming research evidence suggests that the negative symptoms of schizophrenia (NSS) contribute more to impaired quality of life and poor functioning than positive symptoms do (Kurtz, 2005; Kirkpatrick & Fischer, 2006). Primary negative symptoms, including affective flattening, alogia and avolition have a prevalence rate of approximately 20% in patients diagnosed with schizophrenia (Chue, 2013; Cohen et al., 2013). Bobes et al. (2010) conducted an epidemiological study to examine the prevalence of negative symptoms in a sample of 1452 individuals with a clinical diagnosis of schizophrenia according to the DSM-IV criteria. Prevalence of NSS was considerably high and the most frequent negative symptoms (measured with the Positive and Negative Symptoms Scale [PANSS]) were social withdrawal (45.8%), emotional withdrawal (39.1%), poor rapport (35.8%) and blunted affect (33.1%). Furthermore, patients scoring higher in NSS were associated with poorer functioning; individuals who showed higher social withdrawal and poorer rapport were more likely to be unemployed; patients with higher emotional and social withdrawal were more likely to be unmarried/single and last, individuals with higher emotional withdrawal were more likely to receive higher antipsychotic dose. Patel et al. (2014) aimed to examine the profile of individuals with prominent NSS. They retrieved data from a large sample of the case records of 7678 adults with schizophrenia from which they obtained a dataset of 200 cases. These were analysed with the General Architecture for Text Engineering Machine Learning software package to estimate the prevalence of negative symptoms in the whole sample. Results showed that 55.7% of the total sample had at least one negative symptom. Patients with NSS were likely to be males, aged 20 to 29 yrs and single. These patients were likely to have more hospital admissions and exhibit a deterioration of daily functioning.

1.1. Clinical assessment of negative symptoms of schizophrenia

Current treatment with dissimilar antipsychotic drugs addresses mainly the positive symptoms (i.e. psychotic symptoms) of the disorder (Erhart et al., 2006; Buckley & Stahl, 2007). However, psychotic symptoms are not specific to schizophrenia but shared with other disorders such as bipolar disorder, schizoaffective disorder, substance-induced psychosis, and other idiopathic psychotic disorders. Furthermore, treatment-resistant schizophrenia patients do not respond well to antipsychotics (Meltzer & Kostacoglu, 2001) and tend to have more prominent negative symptoms and more severe psychopathology than patients whose condition improves with antipsychotic drugs. Treatment of NSS remains a challenge since there are no guidelines for treating negative symptoms and therefore it is important for a clinician to establish the nature of NSS. Negative symptoms may be primary and therefore related to the core pathophysiology of the disorder, or

secondary, as a derivative of medication or illness duration (Kirkpatrick & Fischer, 2006).

1.1.1. Scale for the Assessment of Negative Symptoms (SANS)

The scale for the assessment of negative symptoms, developed by Andreasen (1989), is a widely used clinician-rated 20-item instrument that measures negative symptoms of schizophrenia. The scale assesses five symptoms: affective flattening, alogia, avolition–apathy, anhedonia–asociality and disturbance of attention. Rabany et al. (2011) support the validity and reliability of the scale to assist clinicians in assessing and separating NSS from positive and depressive symptoms in patients with schizophrenia. A recent study examined the psychometric properties of the SANS scale and the possibility to produce a shorter version of the scale (Levine & Leucht, 2013). Data were re-analysed with item-response analysis (IRT) from a sample consisting of 487 patients with schizophrenia, retrieved from three clinical trials that compared placebo and amisulpride. Comparison of the original and the shorter version of the scale (11 items) showed that the latter had better fit to reliability. The authors concluded that a shorter version of SANS could be used in research settings.

1.1.2. Positive and Negative Syndrome Scale (PANSS)

The PANSS, developed by Kay et al. (1987), is the most widely used tool to assess symptoms of schizophrenia. The subscale for negative symptoms consists of 7 items (blunted affect, emotional withdrawal, poor rapport, passive social withdrawal, difficulty in abstract thinking, lack of spontaneity and stereotypical thinking) that rate from 1 to 7 with a total range score of 7 to 49. One major disadvantage of the scale is that it does not include important domains of negative symptomatology such as motivational and hedonic impairments outside the social environment (Barch, 2013). Moreover, some items such as abstract thinking, stereotypical thinking and poverty of speech appear to address cognitive functioning (Buchanan, 2007). Edgar et al. (2014) examined the reliability and ability of the subscale for negative symptoms of the PANSS to detect change. They retrieved data from a Phase II study of add-on bitopertin therapy in schizophrenia outpatients with prominent negative or disorganized thought symptoms treated with antipsychotics. Data analysis demonstrated validity, adequate internal consistency ($\alpha = 0.71$) and ability to change over time.

1.1.3. Brief Psychiatric Rating Scale (BPRS)

The Brief Psychiatric Rating Scale (Overall & Gorham, 1962) is one of the most frequently used instruments in evaluating psychopathology in patients with schizophrenia. However, the clinical meaning of its total score and cut-off values that are used to define treatment response were unclear (Leucht et al., 2005). The authors aimed to relate BPRS scores to a global clinical judgement by linking BPRS ratings to Clinical Global Impression (CGI) ratings. Results showed that 'Mildly ill' according to the CGI approximately corresponded to a BPRS total score of 31, 'moderately ill' to a BPRS score of 41 and 'markedly ill' to a BPRS score of 53. 'Minimally improved' according to the CGI score was associated with percentage BPRS reductions of 24%, 27% and 30% at weeks 1, 2 and 4, respectively. The corresponding numbers for a CGI rating of 'much improved' were 44%, 53% and 58%. The BPRS addresses emotional withdrawal and blunted affect but fails to assess anhedonia and asociality (Blanchard & Cohen, 2006).

1.1.4. Negative Symptom Assessment (NSA-16)

The NSA developed by Alphas et al. (1989) is an easy to administer 16-item scale that examines the presence and severity of negative symptoms. The scale uses a 5-factor model to describe negative symptoms in terms of communication, emotion/affect, social involvement, motivation and retardation. It has strong psychometric properties (Axelrod et al., 1993). However, like the SANS, it requires time to complete, thus limiting its use in clinical practice. Alphas et al. (2010) aimed to simplify the scale for rapid screening and clinical assessment of NSS.

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