Defining therapeutic benefit for people with schizophrenia: Focus on negative symptoms

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Schizophrenia is a complex, heterogeneous, multidimensional disorder within which negative symptoms are a significant and disabling feature. Whilst there is no established treatment for these symptoms, some pharmacological and psychosocial interventions have shown promise and this is an active area of research. Despite the effort to identify effective interventions, as yet there is no broadly accepted definition of therapeutic success. This article reviews concepts of clinical relevance and reports on a consensus conference whose goal was to apply these concepts to the treatment of negative symptoms.

A number of key issues were identified and discussed including: assessment of specific negative symptom domains; defining response and remission for negative symptoms; assessment of functional outcomes; measurement of outcomes within clinical trials; and the assessment of duration/persistence of a response. The group reached a definition of therapeutic success using an achieved threshold of function that persisted over time. Recommendations were agreed upon with respect to: assessment of negative symptom domains of apathy–avolition and deficit of expression symptoms; thresholds for response and remission of negative symptoms based on level of symptomatology; assessing multiple domains of function including social occupation, activities of daily living, and socialization; the need for clinical trial data to include rate of change over time and converging sources of evidence; use of clinician, patient and caregiver perspectives to assess success; and the need for establishing criteria for the persistence of therapeutic benefit.

A consensus statement and associated research criteria are offered as an initial step towards developing broad agreement regarding outcomes of negative symptoms treatment.

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1. Introduction

Schizophrenia is a complex and multidimensional disorder with an estimated point prevalence of 0.46% (Saha et al., 2005), but which other studies estimate affects up to 1% of the world’s population; and which is a leading cause of disability (Chumakov et al., 2002; Switaj et al., 2012; WHO, 2012). Data from clinical and population-based studies of schizophrenia suggest a lifetime prevalence of severe primary negative symptoms of 15–20%, which increases with age (Buchanan, 2007). Recent analyses of negative symptom dimensions support a division into two clusters of apathy–avolition (AA) and expressive deficits (DE) (Liemburg et al., 2013; Strauss et al., 2013). AA includes amotivation, apathy and social withdrawal (46%); whilst DE includes emotional withdrawal (39%), poor rapport (36%), blunted affect (33%) and poverty of amount and content of speech (Bobes et al., 2010). Negative symptoms are associated with poorer functional outcomes and greater reductions in quality of life (QOL) than positive symptoms (Velligan et al., 1997; Norman et al., 2000; Lysaker and Davis, 2004; Lysaker et al., 2004; Kurtz et al., 2005; Milev et al., 2005; Kirkpatrick and Fischer, 2006). Therefore, targeting the treatment of negative symptoms may have significant functional benefits. It should be noted that
negative symptoms may have sufficient face validity that improvement in these symptoms alone would be sufficient to demonstrate the effectiveness of an intervention and specific assessment of function would not be required for medication registration. (Marder et al., 2013). To date, we do not have an established treatment for negative symptoms (Buckley and Stahl, 2007). However, some pharmacological and psychosocial interventions show promise (Arango et al., 2013; Elias et al., 2013). This is an active area in therapeutic research with a search for “negative symptoms” and “schizophrenia” on Clinicaltrials.gov identifying 93 open and 226 closed, interventional studies (accessed access date December 7th 2014). Given the salience of negative symptoms for functional outcomes and quality of life, developing a definition of a clinically meaningful effect of treatment is needed (Kirkpatrick et al., 2006). There is no consensus in the field of how to define therapeutic “success” in the treatment of negative symptoms. This article will review concepts of clinical relevance (clinically meaningful effect) and then report on a conference whose goal was to apply these concepts to the domain of negative symptoms. (See Fig. 1.)

1.1. Clinical relevance concepts

‘Clinical relevance’, ‘clinical significance’ or ‘clinical importance’ are terms commonly used in an attempt to go beyond statistical significance and determine whether a change, treatment effect or group difference can truly be considered ‘meaningful’. Determination of a statistically significant difference means that the null hypothesis of no difference between the groups can be rejected, because it did not occur by chance. This does not tell us whether the difference is clinically significant or relevant, that is whether an intervention has an effect of practical, real-life importance. Returning to normal functioning in a small sample of participants (both rated by 76% of the respondents) followed by a large effect in a small sample of participants or a small effect in a large sample (Robinson et al., 2005).

Furthermore, there are key differences in the evaluation of clinical relevance for the individual person, versus that for a group, e.g. subjects in a clinical trial. In a clinical visit, therapists or prescribers often assess the relevance for the individual person, versus that for a group, e.g. subjects in a large sample (Robinson et al., 2005). The treatment outcomes considered least important were to improve social life and reduce side-effects. This often depended on the

![Graphical representation of proposed research criteria for the assessment of a therapeutic benefit on negative symptoms of schizophrenia.](image)

1.2. Perspectives on clinical relevance

Some researchers have obtained the views of clinicians, patients and their relatives in order to evaluate clinical relevance. Clinical evaluation forms a critical first step, since a thorough differential diagnosis of possible causes of negative symptoms is necessary to avoid mistaken attribution. This may be especially challenging given the wide range of ‘secondary’ negative symptoms resembling primary negative symptoms, including spurious negative symptoms arising from psychosis, excessive dopamine receptor blockade, depression, Obstructive Sleep Apnea, cortical or subcortical lesions, lack of environmental stimulation, and discouragement/demoralization. Once a diagnosis is established, there is often a disparity between what is considered important to clinicians and what is important to individual patients and their relatives. The literature relating to clinician and patient preferences for treatment and expectations of treatment outcomes shows that clinician and patient perceptions often differ (Montgomery and Fahy, 2001; Kinter et al., 2009). Few studies have been conducted to identify individual priorities in people with schizophrenia. Kinter et al. (2009) conducted focus groups to identify and value endpoints in schizophrenia from an individual perspective using interpretive phenomenological analysis. “Clear thinking” was ranked as important by 80% of participants, followed by “minimization of disease symptoms” and “social activities” (both rated by 76% of the respondents) followed by “daily activities” (60% of respondents). Although the research demonstrated that people with schizophrenia have distinct preferences for treatment and were able to clearly prioritize them, traditional clinical measures may often not reflect their perspective. A similar study was conducted to investigate and compare the value and perceived attainment of treatment goals in schizophrenia among four different groups (patients, relatives, physicians and health technology assessors) (Kuhngik et al., 2012. Overall, twenty treatment goals were identified and then ranked and rated according to their relevance. Patients, physicians and relatives ranked “improved cognitive abilities” among their top three treatment goals. “Reduced disease-related symptoms” was ranked first by relatives and second by physicians. Health technology assessors clearly prioritized outcomes that were more likely to affect costs (i.e., ability to resume work, less hospitalization/need for outpatient visits). All participants ranked goal attainment lower than goal relevance.

Clinician ratings of negative symptoms of schizophrenia have been shown to be poorly correlated with patient ratings, suggesting that clinicians’ perceptions of the patients’ symptoms may differ from the patients’ own perceptions but also raises questions regarding lack of insight (Lasalvia et al., 2002). In addition, there may be differences between clinicians and patients with respect to the domains of negative symptoms and function considered to be relevant. During focus groups, people with schizophrenia have reported a number of treatment goals including increasing energy, improving social relationships, increasing participation in work or other productive activities, and reducing confusion and difficulty concentrating (Fisher et al., 2002; Rosenheck et al., 2005). The treatment outcomes considered least important were to improve social life and reduce side-effects. This often depended on the
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