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Treatment of negative symptoms: Where do we stand, and where do we go?

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ABSTRACT

Negative symptoms, e.g. social withdrawal, reduced initiative, anhedonia and affective flattening, are notoriously difficult to treat. In this review, we take stock of recent research into treatment of negative symptoms by summarizing psychosocial as well as pharmacological and other biological treatment strategies. Major psychosocial approaches concern social skills training, cognitive behavior therapy for psychosis, cognitive remediation and family intervention. Some positive findings have been reported, with the most robust improvements observed for social skills training. Although cognitive behavior therapy shows significant effects for negative symptoms as a secondary outcome measure, there is a lack of data to allow for definite conclusions of its effectiveness for patients with predominant negative symptoms. With regard to pharmacological interventions, antipsychotics have been shown to improve negative symptoms, but this seems to be limited to secondary negative symptoms in acute patients. It has also been suggested that antipsychotics may aggravate negative symptoms. Recent studies have investigated glutamatergic compounds, e.g. glycine receptor inhibitors and drugs that target the NMDA receptor or metabotropic glutamate 2/3 (mGlu2/3) receptor, but no consistent evidence of improvement of negative symptoms was found. Finally, some small studies have suggested improvement of negative symptoms after non-invasive electromagnetic neurostimulation, but this has only been partly replicated and it is still unclear whether these are robust improvements. We address methodological issues, in particular the heterogeneity of negative symptoms and treatment response, and suggest avenues for future research. There is a need for more detailed studies that focus on different dimensions of negative symptoms.

1. Introduction

Negative symptoms in schizophrenia are characterized by marked reductions in goal-directed behavior, which can include speech and social behavior. The lack of activity is reflected in reduced initiative, social withdrawal, anhedonia, affective flattening and poverty of speech, amongst others. One or more negative symptoms are present in approximately 60% of outpatients (Bobes et al., 2010), whereas persistent negative symptoms may be present in 30% of patients with schizophrenia (Kirkpatrick et al., 2006). It should be noted that several issues regarding the definition and boundaries of negative symptoms remain to be further elucidated, and such research will certainly also inform treatment research and practice. For example, the distinction between primary and secondary negative symptoms receives continuing attention in the literature (see also this special issue, articles by Mucci et al., in press and Kirschner et al., in press). A relationship with cognitive dysfunction has been established (Dominguez et al. 2009; Aleman et al., 1999), but the effect sizes are small to moderate. In addition, a relationship with abnormalities of dopaminergic reward systems has been established (Radua et al., 2015).

It is easy to understand that such reductions in activity hamper functioning in daily life, and indeed negative symptoms are associated with poor psychosocial functioning (Lysaker and Davis, 2004). A recent study in 7678 patients found negative symptoms to be associated with increased likelihood of hospital admission, longer duration of admission, and increased likelihood of readmission following discharge (Patel

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et al., 2015). Negative symptoms are therefore an important target for treatment. However, no treatments have as yet emerged to be reliably and robustly effective, as evidenced from large clinical trials. Thus, negative symptoms seem to be more difficult to address than the positive symptoms that define psychotic disorders. This is not to say that no improvements can be achieved at the individual patient level. In this review, we provide an overview of recent research into treatment approaches for negative symptoms by summarizing psychosocial as well as pharmacological and other biological treatment strategies. The goal of this paper was to briefly summarize evidence on current treatments and to highlight novel approaches. To this aim, databases (PubMed and Web of Science) were searched in July 2015 using relevant keywords (e.g., combinations of schizophrenia and negative symptoms with cognitive behav*, psychosocial, antipsychot*, glutamat*, transcranial) to identify papers on psychosocial, pharmacological and neurostimulation trials of schizophrenia.

2. Psychosocial interventions for negative symptoms

Negative symptoms are generally targeted along with other outcome domains in psychological interventions for schizophrenia spectrum disorders. These interventions can be broadly classified into skill-focused interventions, individual psychological interventions, and family interventions.

The most intensively studied skill focused intervention is social skill training (SST). SST targets participants' social functioning by training verbal and nonverbal communication alongside perception and responses to social cues in order to improve their ability to perform in social situations (e.g. Bellack et al., 1997). In a review of outcome studies for negative symptoms 11 controlled trials on SST were identified (Elis et al., 2013). Two of these compared SST to treatment as usual (TAU) and the remaining studies compared SST to an active control group. Five studies found SST to be associated with a change in negative symptoms at post-treatment which was maintained at six-month follow-up in two studies. A recent meta-analysis also found SST to be superior to other interventions ($k = 9$; Turner et al., 2014). Nevertheless both groups of researchers stress the need for further and methodologically improved studies.

Another skill focused intervention is cognitive remediation that targets basic cognitive processes. Although cognitive impairment has often been subsumed under negative symptoms in the past, researchers now widely agree that it is conceptually distinct from negative symptoms (Kirkpatrick et al., 2006). This might explain why, on their own, these interventions have not been found to improve negative symptoms (Elis et al., 2013). However, cognitive remediation combined with components that address social skills or problem solving have produced more promising effects, e.g. Cognitive Enhancement Training (Eak et al., 2013) or the Integrated Psychological Therapy (Roder et al., 2006).

Family interventions differ in characteristics and methods but generally involve providing support to the family and enlisting families as therapeutic agents. They are usually part of a treatment package used in conjunction with routine drug treatment and outpatient clinical management (Dixon and Lehman, 1995). Elements most frequently used are psycho-education, communication training, behavioral problem solving, and crisis management. The majority of studies on family intervention alone or in combination with other interventions demonstrate an improvement in negative symptoms (e.g. Dyck et al., 2000; Elis et al., 2013; Giron et al., 2010, Calvo et al., 2014).

The most widely studied individual psychological intervention is cognitive behavioral therapy for psychosis (CBTp) that aims to support patients in achieving personally meaningful goals by promoting awareness of the links between thoughts, behaviors, and feelings to help implement changes in symptoms and functioning by modifying unhelpful thoughts and self-defeating behavior (NICE, 2009). CBTp was originally developed for positive symptoms, which is why samples in outcome studies were mostly preselected for positive rather than negative symptom severity and negative symptoms are seldom a primary outcome. Meta-analyses of negative symptoms as a secondary outcome nevertheless indicate a significant effect of CBTp for negative symptoms (Velthorst et al., 2015; Wykes et al., 2008). However, the moderate effect size found for the first generation of CBT (Wykes et al., 2008) do not appear to be generalizable to more recent studies (Velthorst et al., 2015). Furthermore, only few studies have focused primarily on negative symptoms. Klingberg et al. (2011) investigated the effect of specifically designed CBT for negative symptoms compared to cognitive remediation in a randomized controlled trial (RCT) including 198 patients diagnosed with schizophrenia and related disorders with at least one negative symptom of moderate severity. The intervention included developing a shared formulation followed by treatment modules addressing different negative symptoms over a mean number of 17.6 sessions. Although both groups improved from pre- to post assessment, negative symptoms did not improve more in the CBTp than in the cognitive remediation condition. Another recent adaptation of CBTp builds on empirical studies that have found negative symptoms to be associated with dysfunctional beliefs (e.g. "Finding new friends is not worth the energy I would have to invest.") (Grant and Beck, 2010), a reduced sense of self-efficacy (Bentall et al., 2010), low expectations of success (Beck et al., 2009), and low self-esteem (Lincoln et al., 2011). Grant et al. (2012) used a cognitive approach to challenge these beliefs in a RCT including 60 patients with psychotic disorders and prominent negative symptoms. They found a significant improvement in functioning at the end of an 18-month period including 50.5 treatment sessions on average. Improvements were found for apathy and avolition but not for anhedonia, flat affect and alogia. In support of the treatment rationale, a subsequent small uncontrolled pilot trial (Staring et al., 2013) that used the same approach over a shorter period of six-months found the pre- to post effect size for negative symptoms to be partially mediated by a change in dysfunctional beliefs. To conclude, CBT may be effective in reducing negative symptoms, but further controlled trials with negative symptoms as a primary outcome are needed.

Direct comparisons of the different interventions in regard to negative symptoms seem to favor SST over other interventions so far (Turner et al., 2014). However, further replications and standardization of measurements and designs are warranted before drawing definite conclusions (Elis et al., 2013). Some evidence suggests that treatment packages that combine several different interventions (e.g. family psychoeducation and skill training) achieve better outcomes than stand-alone interventions (Hogarty et al., 1986). In accord with this finding the recently developed "Motivation and Enhancement Therapy" (MOVE, Velligan et al., 2015) combined environmental support, CBT, skills training, and other components in an attempt to address all domains of negative symptoms. Their preliminary results in an RCT including 51 patients with clinically meaningful negative symptoms suggest that MOVE improves negative symptoms. However, the group differences were not significant until 9 months of treatment and not for all negative symptom scales.

3. Antipsychotics

Only few studies have been designed to evaluate the effects of antipsychotics on negative symptoms as a primary outcome measure (Möller and Czobor, 2015). Most studies into the efficacy of antipsychotics concern acutely ill patients, versus placebo, or compare antipsychotic to each other. These studies often last for 6 to 12 weeks. Improvement of negative symptoms occurs during improvement of positive symptoms in these acutely ill patients. In these studies it is difficult to disentangle whether an effect on negative symptoms concerns primary or secondary negative symptoms (Arango et al., 2004). Primary negative symptoms are those that are not a consequence of other symptoms or medication. When the improvement of initiative and goal-directed behavior is due to a reduction of anxiety, depression, delusions

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