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Review Article

NEGATIVE SYMPTOMS IN SCHIZOPHRENIA : THE PREVAILING CHALLENGES

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Abstract :
Although many advances in the understanding and treatment of schizophrenia have been made many challenges still remain. Most notably is the lack of understanding pertaining to the negative symptoms dimension of schizophrenia and the treatment of such symptomology? Primary negative symptoms affect 20-40% of individuals with schizophrenia and are associated with the greatest impacts upon functional impairment and quality of life. A qualitative review of the prevailing challenges related to the nature, assessment and treatment of negative symptoms was conducted. The current literature in each of the aforementioned areas pertaining to primary negative symptoms was reviewed with a focus upon the key challenges and directions for future research. The results of the qualitative review indicate that the construct of negative symptoms requires further delineation and recent work in the area of the assessment of negative symptoms necessitates further development. In regards to the treatment of negative symptoms no definitive directions are espoused due to the extent of the dearth of knowledge in the area as highlighted in the discussion. The area of negative symptoms research requires multi-disciplinary collaborative research to address the major challenges to the understanding, assessment and treatment of negative symptoms in schizophrenia to improve the quality of life and functional outcomes of those with primary negative symptoms.

Keywords : Schizophrenia, Negative Symptoms, Assessment & Treatment

Introduction :

Over the past decade or so several scientific advances have been made in the fields of genetics, biology and pharmacology in relation to the epidemiology, diagnosis and treatment of schizophrenia and related disorders. Some examples include the exploration of biomarkers and candidate genes in the susceptibility and development of schizophrenia (DeRosse et al., 2008; Javitt, Spencer, Thaker, Winterer, & Hajos, 2008; Pogue-Geile & Yokley, 2010), the identification of structural and functional brain abnormalities (Karlsgodt, Sun, & Cannon, 2010), and the trial of promising new medications in animal models and humans (Patil et al., 2007). None the less, major challenges remain.

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Arguably the most significant and pervasive challenge to the field relates to the dearth of knowledge pertaining to negative symptoms in schizophrenia spectrum disorders. Negative symptoms in schizophrenia are defined as a deficit or diminution of normal functioning (Blanchard &Cohen, 2006; Stahl & Buckley, 2007); historically negative symptomology were conceptualised as the core of the disorder (Bleuler, 1978; Kraepelin, 2009). However since early conceptualisations negative symptoms have long been the neglected symptom dimension in the field (Kaiser, Heekeran & Simon, 2011; Rector, Beck & Stolar, 2005; Turkington & Morrison, 2012) despite the significant functional impairments that are associated with such symptomology.

Schizophrenia in itself is a chronic and debilitating illness that results in high levels of disability and functional impairment (Makinen, Miettunen, Isohanni & Koponen, 2008); with approximately 20-40% of individuals diagnosed with schizophrenia experiencing persistent and enduring negative symptoms (Makinen, Miettunen, Isohanni & Koponen, 2008). It is these individuals with

enduring negative symptoms that are known to have significantly poorer functional outcomes, higher levels of long-term morbidity and greater familial burden than those with prominent positive symptoms (Bowie, Reichenberg, Patterson, Heaton, & Harvey, 2006; Kaiser, Heekeran & Simon, 2011; Kirkpatrick, Fenton, Carpenter & Marder, 2006; Milev, Ho, Arndt, & Andreasen, 2005; Rabinowitz et al., 2012). Further negative symptoms are often more stable and enduring over time than positive symptoms (Velligan et al., 2006). Thus negative symptoms, such as the inability to experience pleasure, social withdrawal, poverty of speech and decreased motivation are often considered a major unmet need in health services and medical research(Alphs, 2006).

The National Institute of Mental Health (NIMH) released a consensus statement on negative symptoms several years ago highlighting areas pertaining to negative symptomology that require further research, clarification and consensus (Kirkpatrick et al., 2006). Seven years on from the release of the consensus statement more work is required in the area of negative symptomology in order to capitalise and advance upon the agreement and developments spawned by the NIMH consensus statement on negative symptoms (Kirkpatrick et al., 2006).

Therefore this paper seeks to highlight key challenges that remain in negative symptom research and identify imperatives for future research. The paper will firstly briefly highlight the heterogeneous nature of schizophrenia in general and the associated challenges. Before highlighting the challenges specific to negative symptomology as they pertain to the nature of negative symptoms as well as their assessment and treatment. Each section will conclude with recommendations for future research. With such research having the potential to facilitate more effective assessment, treatment and management of negative symptoms in schizophrenia and thus the ability to significantly improve the quality of life of the 20-40% of individuals with schizophrenia that experience persistent and enduring negative symptoms.

Brief Overview of the Heterogeneous Nature of Schizophrenia Generally

Schizophrenia itself is a complex and heterogeneous disorder; with positive symptomology, negative symptomology, affective symptomology, disorganization and cognitive deficits all interacting to add to the overall complexity associated with the challenges pertaining to negative symptoms specifically. The complexity of this association is illustrated in Figure 1 below; in this figure it is apparent that all five dimensions overlap with each other as well as intersect altogether.

Thus the complexity of schizophrenia as highlighted in the diagram above is associated with several prevailing challenges; these challenges are summarised in Box 1 below. The first challenge pertains to the nature of the psychopathology associated with schizophrenia being truly dimensional in nature; however the nomenclature attempts to categorise and award pseudo boundaries to the symptomology. Similarly the second challenge relates to the issues associated with quantifying a phenomenon that is in fact qualitative in nature; that is all individuals' experience schizophrenia differently making quantification of the dimensions problematic.

The third challenge pertains to the lack of a specific treatment goal or target for treatment in the treatment of schizophrenia. That is psychiatric diagnoses are symptom based as such treatment is symptom based; hence the true underlying dimension is not being targeted in treatment. The last challenge noted above is the false assumption that schizophrenia results from a single aetiology rather than as a result of multiple aetiologies. Or distinctive aetiologies associated with each of the dimensions outlined above. These challenges; reflective of the nature of schizophrenia and our understanding of the disorder further complicate the assessment and treatment of schizophrenia generally as well as impacting upon the negative symptom dimension specifically.

Box 1. The Prevailing Challenges in Schizophrenia

The Challenges
Dimensional versus Categorical Nature of Schizophrenia
Quantifying a Phenomenon that is Truly Qualitative in Nature
Lack of Specific Treatment Goal in Schizophrenia
The Pseudo-Assumption of a Single Aetiology of Schizophrenia

Figure 1. The Heterogeneous Nature of Schizophrenia

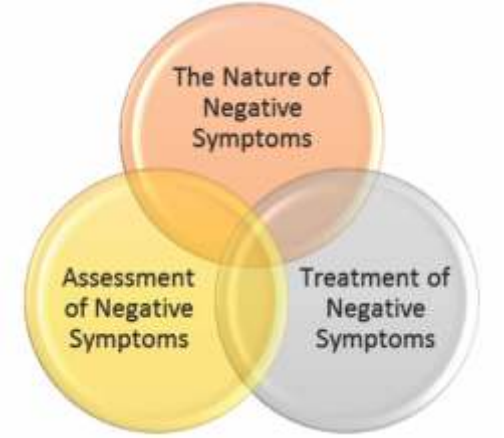

Figure 2. The Inter-Relatedness of the Key Challenges in Negative Symptom Research

Negative Symptoms: The Key Challenges

The following section summarises the current state of knowledge pertaining to negative symptoms; highlighting the key challenges and gaps in the area. Broadly there are three key challenges: firstly; what is the nature of negative symptoms, secondly; challenges pertaining to the assessment of negative symptoms and thirdly; challenges relating to the treatment of negative symptoms. Similarly to the nature of schizophrenia in general, these challenges pertaining specifically to negative symptoms are not independent with each of the aforementioned challenges being inter-related and as such hindering progress in each of the respective areas. The inter-relatedness of these challenges is illustrated in Figure 2 below. Further it is the author's viewpoint that the abovementioned order accorded to the key challenges in negative symptoms research highlights the hierarchical nature in which these would most effectively be addressed with research in each area informing research within the subsequent domains.

What is the Nature of Negative Symptoms?

A lack of consensus and consistency in the negative symptomology construct has continued to hinder research efforts in the area. Fundamentally there remains uncertainties in the symptoms' that comprise the negative symptom dimension (American Psychiatric Association, 2000; Kirkpatrick, 2006; Arango & Carpenter, 2011).

With the DSM-IV-TR (American Psychiatric Association, 2000) listing affective flattening (blunted affect), alogia and avolition as negative symptoms with anhedonia noted as an associated feature of schizophrenia. In contrast Arango and Carpenter (2011) ascertain that asociality and apathy along with anhedonia are commonly also acknowledged to be negative symptoms in addition to affective flattening (blunted affect), alogia and avolition. Kirkpatrick and colleagues (2006) in the NIMH consensus statement on negative symptoms agreed that asociality, blunted affect, alogia, anhedonia and avolition currently constitute the negative symptom dimension. These symptoms acknowledged by the NIMH consensus statement on negative symptoms are defined in Table 1 below.

Table 1. Definitions of Negative Symptoms

Negative Symptom	Definition*
Blunted Affect	Reduced emotional expression and expressiveness.
Alogia	Poverty of speech or poverty of content of speech.
Avolition	Lack of volitional action.
Asociality	Lack of interest in social contact and experiences.
Anhedonia	Inability to experience pleasure.

*Definitions of symptoms' in the table above are derived from Arango and Carpenter (2011).

In addition to the symptoms that comprise the negative symptom dimension of schizophrenia there are also questions pertaining to the factor structure of the construct (Blanchard & Cohen, 2006; Kirkpatrick & Fisher, 2006). For example is the construct of negative symptoms in schizophrenia uni-dimensional or multi-dimensional in nature (Blanchard & Cohen, 2006; Kirkpatrick & Fisher,

2006). If the construct is multi-dimensional what is the factor structure that underlies the construct (Blanchard & Cohen, 2006; Kirkpatrick & Fisher, 2006).

Recently Messinger and colleagues (2011) in a theoretical review suggested that the symptoms of avolition and affective deficits constitute the negative symptom domain. Similarly Horan and colleagues' (2011) found a two factor solution for a recently developed measure of negative symptoms; the Clinical Assessment Interview for Negative Symptoms (CAINS). Specifically the factor structure could be broadly distinguished between experiential and expressive items (Horan et al., 2011). Furthermore in light of the aforementioned issues further clarification of the nosology of negative symptomology is also needed (Linscott & van Os, 2006; Parnas, 2011). As such clarification is paramount to not only diagnosis, but also; to research in general and more importantly the meaningful interpretation and translation of results of empirical studies into clinical practice (Erhart, Marder & Carpenter, 2006).

In addition to the aforementioned issues and lack of consensus pertaining to negative symptomology some researchers have even conjectured that the disease entity (schizophrenia) marked by primary negative symptomology is not simply a distinct dimension rather it indicates the presence of a separate disease; not schizophrenia (Carpenter, 2006; Carpenter, 2007; Kaiser, Heekeren & Simon, 2011). As factor analytic research commonly supports the notion of schizophrenia spectrum disorders being multi-dimensional in nature however inconsistencies to the factor structure of schizophrenia in general remain (Lindenmayer, Grochowski & Hyman, 1995; Toomey et al., 1997; Peralta & Cuesta, 2001; Blanchard & Cohen, 2006).

Similarly others have questioned the definition of negative symptoms (Messinger et al., 2011). With Messinger and colleagues (2011) highlighting that defining negative symptoms as a diminution or deficit of normal functioning as problematic due to the current understanding of cognitive processes in schizophrenia. However it should be noted that this is the definition commonly utilised and endorsed by the NIMH consensus statement on negative symptoms (Kirkpatrick et al., 2006) and as such the definition adopted in this article. However, future questioning and reframing of the definition based upon strong empirical support may be needed.

Thus it is clearly apparent that there remains a general lack of consensus pertaining to the nature of negative symptoms in schizophrenia. Table 2 below highlights some of the key challenges in the area and the actions that are required as well as the potential implications of such research. Future research should seek to delineate and validate an empirically founded definition of negative symptoms as well as clarifying the nosology of negative symptoms. Further the symptoms that comprise the negative symptom domain and the factor structure of the negative symptom domain also require clarification, delineation and consensus. Specifically, Erhart, Marder and Carpenter (2006) recommend the delineation of whether negative symptoms are homogenous or heterogeneous as well as categorical or dimensional. Such work will greatly benefit the advancement of research endeavours aimed at developing and improving the assessment and treatment of negative symptomology in schizophrenia.

Table 2. The Nature of Negative Symptoms: Challenges, Actions Required & Implications

Challenge	Research / Action Required	Implications
Consistency in the definition of the domains of negative symptoms	Adoption of the NIMH Consensus Statement of Negative Symptom domains (Kirkpatrick et al., 2006)	Consistency in research & clinical practice; assisting with making the translation of research into clinical practice more straight forward.
	Nomenclature for diagnosis that encompasses these domains	

Challenge	Research / Action Required	Implications
Identifying the true boundary conditions of the negative symptom construct	Research to ascertain whether the five domains specified by Kirkpatrick et al. (2006) are the true boundaries of the negative symptom construct.	An understanding of the true boundary conditions and structure of the construct has the potential to advance assessment and treatment.
	Theorising as to the structure of the negative symptom construct.	
Consensus on the definition of negative symptoms	Research to clarify whether the current definition of negative symptoms is flawed due to our emerging understanding of cognitive problems in schizophrenia (Messinger et al., 2011).	Clarification and delineation of the relationship between negative symptoms and cognition in schizophrenia has the potential to lead to treatment interventions for both issues. As well as the potential to inform early intervention strategies.

The Assessment of Negative Symptoms

The very nature of negative symptoms makes assessment difficult for researchers and clinicians alike. Negative symptoms are insidious and represent an absence or reduction of usual behaviours often making them difficult for clinicians to recognise and diagnose (Buckley & Stahl, 2007). Moreover negative symptoms can also impede the individual's ability to communicate their inner experiences and psychopathology (Fanous et al., 2012). Likewise there are also problems associated with detecting improvements in negative symptomology over time (Stahl & Buckley, 2007).

Negative symptoms are not uni-factorial in origin (Toomey et al., 1997), nor are they commonly considered to represent a homogenous entity (Blanchard & Cohen, 2006). Thus the distinction between primary negative symptoms; those that intrinsically reflect the core symptoms of the disorder itself, and secondary negative symptoms; those that result from other factors such as the effects of antipsychotic treatment, positive symptoms, extrapyramidal symptoms, depression or environmental under-stimulation remains elusive (Flaum & Andreasen, 1995; Messinger et al., 2011). Further few have used diagnostic and assessment scales to attempt to distinguish between primary and secondary negative symptoms. Thus, it is often unclear in antipsychotic outcome studies the origin of the negative symptoms that are responding (or not responding) to treatment (Murphy, Chung, Park, & McGorry, 2006).

The assessment of negative symptoms is intimately linked to the conceptualisation of the nature of negative symptoms (as discussed in the section above) with the nature of negative symptoms being reflective of how they are assessed. Factor analysis of two of the most commonly utilised instruments for the assessment of negative symptoms as suggested by Erhart, Marder and Carpenter (2006); the Scale for the Assessment of Negative Symptoms (SANS: Andreasen 1982; Andreasen, 1983) and the Schedule for Deficit Syndrome (SDS: Kirkpatrick et al., 1989) indicate that they both assess more than a single factor. Suggesting that negative symptoms are multi-dimensional in nature; well at least how they are conceptualised and measured by the two aforementioned instruments (Erhart, Marder & Carpenter, 2006).

Further the shortcomings of another commonly utilised instrument for the assessment of negative symptoms the Positive and Negative Syndrome Scale (PANSS: Kay, Fiszbein & Opler, 1987) have also been emphasized (Blanchard et al., 2010). A summary of some of the criticisms of the PANSS are displayed in Box 2 below. For example the PANSS is exclusively reliant upon behaviour observed during the process of the interview as well as the carer's perspective; thus the ratings are devoid of the individual with schizophrenia perspective (Blanchard et al., 2010). Particularly troublesome is the lack of perspective that can be provided by the client in response to experiential deficits (Blanchard et al., 2010; Forbes et al., 2010). Overall Blanchard and colleague's (2010) article highlighted the limitations of the previously mentioned measures of negative symptoms. Specifically that overall the

instruments are out-dated and do not reflect the contemporary understanding and current empirical findings pertaining to negative symptoms (Blanchard et al., 2010).

Box 2. Criticism of the PANSS

Criticisms of the PANSS
The clinical implications of the PANSS scores are unclear (Leucht et al., 2005).
The clinical meaning of the response cut-off scores employed in clinical trials is also unclear due to the aforementioned issue (Lancon et al., 1998; Leucht et al., 2005).
Key conceptual limitations. For example individual items reflect several conceptually distinct domains (Blanchard et al., 2010).
Behavioural measurement of experiential deficits (Blanchard et al., 2010).
Uncertain factor structure (Lancon et al., 1998).

The shortcomings of existing instruments summarised above is in accordance with the National Institute of Mental Health (NIMH) consensus statement on negative symptoms suggestion for the development of a new measure of negative symptomology in schizophrenia (Kirkpatrick et al., 2006; Blanchard et al., 2010). As the current instruments were impeding advancements in the treatment of negative symptoms (Forbes et al., 2010).

As such a panel of experts convened and collaborated to develop a new measure of negative symptoms to overcome the shortcomings of the existing measures (Forbes et al., 2010; Horan et al., 2011). It quickly became apparent that two instruments were required to remedy the current void that existed in the measurement of negative symptoms specifically a longer more detailed instrument as well as a brief concise instrument suitable for clinical trials (Kirkpatrick et al., 2011). Thus the CAINS (Forbes et al., 2010; Horan et al., 2011) and the Brief Negative Symptom Scale (BNSS: Kirkpatrick et al., 2011; Strauss et al., 2012) were developed to meet both of the aforementioned challenges respectively.

The CAINS was developed to measure the five domains of negative symptoms espoused by the NIMH consensus statement on negative symptoms specifically; anhedonia, asociality, avolition, alogia and blunted affect (Forbes et al., 2010; Horan et al., 2011). However Forbes and colleagues (2010) note that the latent structure of negative symptoms remains undetermined. The development of the CAINS also sought to overcome the reliance on behavioural and performance deficits that existed in the current scales thus neglecting experiential deficits that can be considered the core of the negative symptom construct (Forbes et al., 2010). Thus the CAINS incorporates measures of experiential deficits (Forbes et al., 2010; Horan et al., 2011). Further the CAINS is in line with current empirical research on motivation and hedonic experience in schizophrenia; as it includes measures of both anticipatory and consummatory pleasure (Strauss et al., 2011; Forbes et al., 2010; Horan et al., 2011). Recently Barch (2013) suggested that use of instruments such as the CAINS assists with integrating our current understanding of affective neuroscience into the assessment of schizophrenia.

The initial results from the early development and validation study of the CAINS showed overall support for the feasibility and validity of the instrument (Forbes et al., 2010). However there were issues pertaining to the measurement of the intensity of hedonic experience in a population with vocabulary impediments and limited speech output (Forbes et al., 2010). Furthermore there were also issues evident in the measurement of asociality specifically concerning how best to integrate the information about different social relationships (family, romantic and friendships) to improve the consistency of the scale (Forbes et al., 2010).

A factor analysis of preliminary CAINS data; has indicated a two factor structure to the negative symptom dimension (Horan et al., 2011), namely; an experiential factor and an expressive factor. With the experiential factor, being composed of the symptoms of; avolition, anhedonia and asociality and the expressive factor comprised of; blunted affect (affective flattening) and alogia (Horan et al., 2011). Horan and colleagues (2011) concluded that the CAINS is displaying promising potential as a measure for the assessment of negative symptoms.

Although the CAINS is displaying promise not all individuals

with schizophrenia have negative symptoms and as such assessment by the full CAINS is not always feasible and pragmatic (Park et al., 2012). With methods that can quickly and efficiently screen patients that may require further assessment being both practical and efficient. As such Park and colleagues (2012) recently developed and trialled at brief self-report version of the CAINS (CAINS-SR). The results indicated that the experience subscale was psychometrically sound whereas the expression subscale exhibited poorer psychometric properties (Park et al., 2012). Nonetheless the authors concluded that the preliminary results indicated the potential of the CAINS-SR with further work and validation (Park et al., 2012).

In addition to the development of the CAINS and the CAINS-SR the original expert panel sought to develop a concise measure of negative symptoms; specifically a measure that would be appropriate for use in both inpatient and outpatient clinical trials and sensitive to change over time (Kirkpatrick et al., 2011). Thus the Brief Negative Symptom Scale (BNSS) was developed (Kirkpatrick et al., 2011; Strauss et al., 2012). Following from the CAINS the BNSS also sought to measure the five domains of negative symptoms, to employ a distinction between anticipatory and consummatory experience of pleasure as well as a differentiation between internal experiences and behaviour (Kirkpatrick et al., 2011). Further in addition to being concise; so the measure is feasible for use in large multi-centre clinical trials, Kirkpatrick and colleagues (2011) also aimed for the items to be cross-culturally valid and the measure to be suitable for use in other trials (such as epidemiological and psychological research).

The BNSS in addition to measuring the five domains of negative symptoms specified by the original NIMH consensus statement on negative symptoms (Kirkpatrick et al., 2006) also incorporates a measure of distress (Kirkpatrick et al., 2011; Strauss et al., 2012). The measure of distress or lack of normal distress is included in an attempt to differentiate between those that are suffering from primary and secondary negative symptoms (Kirkpatrick et al., 2011). However further study is required to ascertain whether the item meaningfully differentiates between the two aforementioned populations (Kirkpatrick et al., 2011).

Similar to the CAINS the BNSS was also found to have a two factor structure in Kirkpatrick and colleague's (2011) preliminary study. Recently Strauss and colleague's (2012) conducted a study to further test the factor structure of the BNSS. The results also indicated a two factor structure similar to the CAINS with one factor reflecting amotivation and pleasure and the other factor indicative of emotional expression (Strauss et al., 2012).

In sum it is clearly apparent that recent efforts have seen the development and as such advancement in the assessment and measurement of negative symptoms. However additional research is necessary to further test and validate the psychometric properties of the newly developed measures coupled with further delineation of the boundaries of the negative symptom construct. Moreover efforts need to be made to consolidate upon the gains accomplished through the development of new measures for the assessment of negative symptoms. Key challenges in the area of the assessment of negative symptoms are detailed in Table 3 below.

The Treatment of Negative Symptoms

Currently there exists no agreed upon, empirically founded efficacious treatment for enduring (or primary) negative symptoms in schizophrenia (Kreyenbuhl et al., 2010). With most antipsychotic trials generally focusing on positive symptoms as the primary outcome measure (Tarrier & Wykes, 2004), and few assessing the overall reduction in negative symptomology and even fewer evaluating the effects on the symptoms independently. As such the PORT recommendations for the treatment of schizophrenia do not make any recommendations regarding the treatment of negative symptoms as to date no pharmacological or psychological treatment has been found to be consistently effective in the treatment of negative symptomology (Kreyenbuhl et al., 2010).

Challenge	Research / Action Required	Implications
Consistency in the assessment of negative symptoms	Adoption of the new measures (CAINS, BNSS) to assess negative symptoms both in research and clinical practice.	Facilitate the comparative evaluation of different research studies and aid in the translation of research into clinical practice.
Psychometric validation of the new measures of negative symptoms	Clarify and validate the psychometric properties of the CAINS and BNSS.	Advancement of the field of negative symptoms research through the provision of psychometrically sound measures of negative symptoms.
Differentiation of primary and secondary negative symptoms	Test the efficacy of distress in delineating between primary and secondary negative symptoms.	Delineation of the difference between primary and secondary negative symptoms will assist with the development of treatments to target primary negative symptoms.
	Theorise and test other modes for the delineation between primary and negative symptoms.	

Although both first and second generation antipsychotics have generally been highly effective in the treatment of positive symptomology they are minimally effective in the treatment of the negative domains of schizophrenia (Tandon, Nasrallah & Keshavn, 2010). First generation anti-psychotics or conventional neuroleptic treatments have demonstrated negligible efficacy in the treatment of negative symptoms (Kelley, Haas, & van Kammen, 2008; Tandon, Nasrallah & Keshavan, 2010). Some second generation or atypical antipsychotics have demonstrated small effect sizes for the treatment of negative symptoms in clinical trials (Buchanan et al., 2007; Kelley, Haas, & van Kammen, 2008). However it remains unclear whether this reduction in negative symptoms is indicative of a reduction of secondary negative symptoms through reducing positive and depressive symptoms. Tandon, Nasrallah and Keshavan (2010) argue that much of the effect of antipsychotics upon negative symptoms is resultant from a reduction of psychotic symptoms thus targeting secondary negative symptoms not enduring primary negative symptoms. Further they ascertain that antipsychotics have no demonstrable efficacy against primary negative symptoms or deficit syndrome (Kirkpatrick et al., 2006; Tandon, Nasrallah & Keshavan, 2010).

Similarly a recent meta-analysis indicated that the augmentation of antipsychotic therapy with an anti-depressant was more effective than an antipsychotic alone in the treatment of negative symptoms (Singh et al., 2010). Thus the addition of the anti-depressant may be targeting secondary negative symptoms and/or depressive symptoms (masked as negative symptoms) as oppose to primary enduring negative symptoms. Further in addition to antipsychotic therapy several other pharmacological strategies have been evaluated for the treatment of negative symptoms with some success thus far according to Tandon, Nasrallah and Keshavan (2010). Agents that stimulate the NMDA glutamate receptor in combination with antipsychotics have demonstrated some efficacy in the amelioration of negative symptoms (Tandon, Nasrallah & Keshavn, 2010). Further treatments that target the metabotropic glutamate receptors have also shown some success (Tandon, Nasrallah & Keshavn, 2010).

Recently Noroozian and colleagues (2013) tested the efficacy of the augmentation of risperidone treatment with tropisetron an anti-emetic drug for chemotherapy-induced and postoperative emesis for the treatment of primary negative symptoms. The results indicated that the tropisetron addition to treatment improved the primary negative symptoms of individuals with chronic stable schizophrenia. Thus the preliminary results support the efficacy of this addition to risperidone and further research should be conducted to verify theses preliminary results.

Despite the lack of empirical data, clinical guidelines indicate the most effective treatment for schizophrenia generally is a continued care approach incorporating antipsychotic medication and psychosocial intervention such as cognitive behavioural therapy, social skills training,

family interventions and supported employment (Lehman, Lieberman, Dixon, & et al., 2004; Mojtabai, Nicholson, & Carpenter, 1998). However, real world studies in hospital and community settings demonstrate that this rarely occurs (Drake, Bond, & Essock, 2009; Mojtabai et al., 2009). Furthermore even when combined pharmacological and psychological treatment is offered; participation of individuals with prominent negative symptoms may be difficult to facilitate and less efficacious due to the inherent nature of negative symptoms (Whittington, Barnes & Kendall, 2010).

A variety of psychosocial individual and family treatment programs have been developed and trialled for their ability to reduce symptoms (in conjunction with antipsychotic treatment) and have demonstrated modest effects in comparison to treatment as usual for negative symptoms (Klingberg et al., 2011; Pfammater, Junghan, & Brenner, 2006; Thorup et al., 2005). Recently Staring, ter Huurne and van der Gaag (2013) in a small pilot study found a cognitive behavioural therapy treatment aimed at targeting negative symptoms to be modestly effective in reducing negative symptomology; therefore further research is needed. However, the delivery of these services to community patients is hindered by financial, workforce and regulatory constraints within mental health systems. In addition to pharmacological and psychological interventions for the treatment of negative symptoms repetitive transcranial magnetic stimulation (rTMS) has also been trialled and is demonstrating some promise for the reduction of negative symptoms (Dlabac-de Lange, Knegtering & Aleman, 2010; Tandon, Nasrallah & Keshavan, 2010).

In sum it is apparent that largely negative symptoms remain untreatable; especially primary negative symptoms. As such concerted efforts need to be made to develop both pharmacological and psychological inventions that will reduce not only secondary negative symptoms but more importantly primary negative symptoms; due to the high level of functional impairment that such symptomology imposes. Akin to this challenge is the need to be able to differentiate between primary and secondary negative symptoms in order to advance treatment prospects. Recently Bell and colleagues' (2013) based upon the results of their empirical study recommended that separate treatments both pharmacological and psychosocial, be developed for negative symptoms and social cognition. Similarly Strauss and colleagues' (2013) recently conducted a study assessing whether negative symptoms are multi or uni-factorial. The results of their study indicated two separate domains and unique negative symptom profiles; in accordance with the domains measured by the BNSS and CAINS. Therefore they recommended that future studies aiming to develop pharmacological treatments for negative symptoms should attempt to treat these domains of negative symptomology separately. As without reducing the heterogeneity of negative symptoms; attempts to develop and treat negative symptoms will remain challenged (Strauss et al., 2013).

As reviewed above it is apparent that some novel approaches such as agents that target the glutamate receptors and rTMS are demonstrating some success in the treatment of negative symptoms. As such further work is needed to both advance these novel approaches as well as clarify the negative symptoms they are targeting (primary or secondary) as well as the negative symptom domains that they are effective in reducing. Thus due to the extent of the dearth of knowledge in this area no specific recommendations can be made for future research. Rather efforts need to be made generally to develop and test treatments both pharmacological and psychological for the treatment of primary negative symptoms.

Conclusion :

Important progress in research and translational research in particular has influenced practice in the treatment of schizophrenia in general. However the issues outlined in this paper above highlight the pressing need for research within the area of negative symptoms. Not only should research focus on the uncertainties in the negative symptom construct, the assessment of negative symptoms

as well as their treatment but efforts should be made also to minimise the gap between evidence based intervention and health service delivery (Drake & Essock, 2009).

Schizophrenia is a multifactorial and complex disorder, and no discipline has the skills, capacity and resources to fully address the challenges outlined above in order to improve the understanding and treatment of primary negative symptomology in schizophrenia. Therefore multidisciplinary collaborative research is necessary to address the challenges evident pertaining to negative symptoms. As the area requires research that can only be conducted through the collaborative involvement and information sharing of scientists from various disciplines, along with health professionals from the community as well as mental health consumers. Although the process of collaboration is not simple, with a number of significant barriers that inhibits the collaborative process. Efforts need to be made to overcome these barriers to address the dearth of knowledge regarding the nature, assessment and treatment of the negative symptoms in schizophrenia and hence improve the quality of life of individuals with schizophrenia who experience primary negative symptoms.

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