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Negative Symptoms- an Update

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ABSTRACT

Negative Symptoms in psychiatry are deficits in experience and behavior that are attributed to loss of functions of brain. Negative symptoms have been conceptualized as the core aspect of schizophrenia and have been recognized as important ever since the days of Griesinger, Kraepelin and Bleuler. But over the years the significance of the negative symptoms was deleted and emphasis was placed almost exclusively on positive symptoms. The return of negative symptoms in schizophrenia was inevitable. The five general categories of negative symptoms include avolition, anhedonia, affective blunting, alogia and asociality. The subdomains of negative symptoms are experience domain (avolition and anhedonia) and expressivity domain (affective blunting and alogia).

In this review article the authors discuss the evolution of the concept, the current conceptualization, consensus general categories and subdomains of negative symptoms, the relationships to symptoms of other domains, negative symptoms in the different phases of schizophrenia, Primary Enduring Negative Symptoms (PENS) and Persistent Negative Symptom (PNS), the nonspecific, specific and new generation scales for assessment. The clinical importance of negative symptoms in terms of diagnosis, prognosis and treatment options, the impact on comprehension of neurobiology of schizophrenia and the resultant modifications in clinical and etiological models of schizophrenia are discussed. Further the authors briefly discuss negative symptoms in other psychiatric disorders.

Keywords: Negative Symptoms, Deficits, Core of Schizophrenia, Category, Sub-domain.

INTRODUCTION

Negative symptoms (NS) are abnormal absence of normal behaviour and experience, attributed to the loss of normal functions of the brain. The NS are defined as absence of experience/behaviour that should have been present. [1] They are general descriptive terms used for the various clinical manifestations of the diminished capacity for ordinary behavioural functioning (behavioural deficits). [2] Though there are differences in the language used to refer to NS such as, deficits symptoms, defect state symptoms, type II symptoms, core symptoms, fundamental symptoms, primary symptoms and basic symptoms, there are definite consensus about its clinical significance. [3-7] The NS are important in the diagnosis, prognosis as well as in understanding the neurobiology of schizophrenia. [4,7] The NS and the cognitive deficits are considered as the core aspects of schizophrenia. [3-7] In ICD-10 and DSM5 the NS are neither necessary nor sufficient for diagnosis of schizophrenia. The primary enduring NS (PENS) and the persistent NS(PNS) predict poor outcome in patients with schizophrenia. The concept of NS challenged the then existent frontiers and concepts of schizophrenia. This paved way for researchers to develop new models of schizophrenia and new biological and neurological explanations for schizophrenia. The concept of NS was reintroduced to psychiatry in 1974. [2] Since early 1980's there has been a rekindled interest in NS among schizophrenia researchers. [3-7] This renewed interest resulted in the

development of competing concepts, assessment methods, biological and neurological models and new treatment options for schizophrenia. [3,7]

EVOLUTION OF THE CONCEPT

Recognizable descriptions of the NS of schizophrenia can be found as early as the mid-1800s, with Griesinger's descriptions of an "absence of will," followed by Kraepelin's description of a "weakening of volition" among some people with schizophrenia. Since Emil Kraepelin and EugenBleuler consolidated the concepts of dementia praecox and schizophrenia, it has been recognized that the disorders are heterogeneous. Clinicians and investigators had struggled to find out the core symptoms of schizophrenia. NS were given a more prominent place in the earlier concepts of schizophrenia. Emil Kraepelin in his writings on dementia praecox described the 'avolition syndrome' as characteristic of the disorder. Emotional dullness, loss of inner sympathy, loss of interest, loss of motivation, loss of goal directed movements and deterioration were described as core aspects of dementia praecox. EugenBleuler described emotional deterioration as characteristic of schizophrenia. He recognized that the fundamental symptoms (primary symptoms) were more important for diagnosis of schizophrenia than delusions and hallucinations. The primary symptoms (4As) have very strong resemblance to the current NS. [3,7] Kurt Schneider described emotional withdrawal and lack of empathy as characteristic features of schizophrenia. But he did not include such symptoms in his First Rank Symptoms.

Both Kraepelin and Bleuler considered NS as fundamental or core psychopathology of schizophrenia. But over the years the significance of the NS was brought down and emphasis was placed almost exclusively on positive symptoms like delusions, hallucinations, formal thought disorders and catatonic symptoms. This fact is evidenced by the universal acceptance of Schneider's FRS as soon as it was published. First Rank Symptoms consist of exclusively positive symptoms and they became so popular that most of the diagnostic criteria for schizophrenia were based exclusively on the presence of the FRS until recently. The reasons for the neglect of the NS described as core features by Kraepelin and Bleulermay include the following; the florid expression and manifestations of the positive symptoms, the dramatic response of positive symptoms to dopamine receptor antagonists, the fact that it is easier to define, assess and document positive symptoms compared to the NS and the universal popularity of the FRS. In addition to the views of Kraepelin and Bleuler, the concept of 'Institutionalization'(Wing 1970) and Barton's Neurosis(Institutional Neurosis) were major influences in support of NS. [5-7] The return of NS in schizophrenia was inevitable because of their universal presence and endurance and the fact that the positive symptoms failed to explain chronic state, deterioration, residual phase, disability and treatment refractoriness. [3]

It is generally held that John Hughlings Jackson introduced the negative and positive symptom concept to neurology (1875, 1889). This was done based on his complex hierarchical organization theory of the brain. Berrios (1985) in his historical review remarks that it was in fact John Russell Reynolds (1857) who introduced the NS to neurology. [8] Reynolds's concept of NS was not based on any theory as such. It is generally believed that the NS were reintroduced to psychiatry by Strauss and Carpenter (1974). HoweverBerrios mentions that it was De Clerambault (1942) who introduced the concept to psychiatry and Crow remarks that it was introduced to psychiatry by Snezhenesky(1968). [8] It is generally accepted that the reintroduction of NS and the initial semantic work was done by Strauss et al (1974), the empirical research was kicked off by Crow(1980) and the initial codification was completed by Andreasen (1981, 1982). [1-4,9] Mathai and

Gopinath introduced NS to psychiatric research in India during 1982-84. [3,6,7,10]

CURRENT CONCEPTULIZATION

Most of the current investigators have used the concept of NS to refer to the reduction or loss of normal functions. The current concept is descriptive, not based on theories and does not imply neurobiology or relationship to other symptoms. Hence it could be argued that the current concept is more Reynoldian than Jacksonian. The NS include signs and symptoms pertaining to affective, cognitive, volitional and social behaviour domains of the higher functions of the brain. They indicate the loss of emotional experience, conceptual fluency, the experience of pleasure, volition and ability for interpersonal relationship. [3]

There is no unanimity on the number, category and components of NS. The list of NS given in Scale for Assessment of NS(SANS), Positive And Negative Syndrome Scale(PANS), Schedule for the Deficit Syndrome(SDS),ICD-10 and DSM 5 are more or less similar, but not exactly the same. As a matter of fact some of the components in SANS and PANS are positive symptoms. The NS in SANS include affective blunting/ flattening, alogia, avolition, apathy, anhedonia, asociality and attention impairment (seven As). [9,10]

Apathy and attention impairment are not accepted by other researchers as NS. Blunted affect, emotional withdrawal, poor rapport, passive/ apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneous flow of conversation and stereotyped thinking are the NS in PANS. But difficulty in abstract thinking and stereotyped thinking are considered as positive symptoms by other investigators. [11] Restricted affect, diminished emotional range, poverty of speech, curbing of interest, diminished sense of purpose and diminished social drive are the NS in SDS. [12-14] Marked apathy, paucity of speech and blunting/ incongruity of emotional responses usually resulting in social withdrawal and lowering of social performance and not attributable to depression or neuroleptic medication are the ICD-10 NS of schizophrenia. The DSM 5 includes diminished emotional response and avolition as characteristic NS of schizophrenia.To reduce the differences in this area the consensus conference of experts on NS held in the NIMH in 2005 described five general categories of NS. They are Avolition, Anhedonia, Affective Blunting, Asociality and Alogia. [15] Avolition and Anhedonia are the most common NS. During the conference the two possible subdomains within the NS were discussed and agreed upon by the experts. [16]

Five General Categories of NS

Avolition means loss of will or drive. The term may be considered as having almost similar meaning to abulia in neurology. Avolition and apathy are closely related concepts. Avolition is deficit in ability to act whereas apathy is the lack of concern for an idea or task. Avolition is the inability to initiate and persist in goal directed activities. When severe enough to be considered pathological, avolition is pervasive and prevents the person from completing many different types of activities (examples: work, intellectual pursuits and self-care). [17]

Anhedonia specifically refers to a loss of ability to experience joy and pleasure, a deficiency which is pervasive. [18] Anhedonia is the loss of ability to find or derive pleasure out of activities or relationships. It is manifested as pervasive loss of interest and pleasure. It is reported as the most persistent of NS in schizophrenia. According to DSM 5 anhedonia is lack of enjoyment from, engagement in or energy for life's experiences; deficits in the capacity to feel pleasure and take interest in things. Anhedonia is a facet of the broad personality trait domain detachment. [17] Anhedonia is one of the most characteristic diagnostic criteria for depressive disorder in both ICD-10 and DSM5. Anhedonia is also described in schizophrenia. Deconstructed into its component parts, the anhedonia in schizophrenia is reported to be

disproportionately more conspicuous in anticipatory hedonic experience deficit and social specific hedonic deficits. [18]

Affective Blunting is Inability to understand and recognize displays of emotion from others and an inability to express emotion. It is manifested with significant reduction in intensity of affect and consequent reduction in range and reactivity of affect. There may be deficits in tone of voice, facial expressions, gestures, prosody and understanding the social signals. Affective Flattening is a more severe degree of blunting manifested with unresponsive and immobile face, poor eye to eye contact and reduced body language. Blunted affect is significant reduction in the intensity of emotional expression in DSM5.

Asociality is the passive or apathetic social withdrawal manifested with indifference to social relationships, decrease in drive to socialize, decrease in sexual desire and interest and inability to feel intimacy and closeness. According to DSM 5 asociality is reduction in initiative for interacting with other people.

Alogia includes loss of production of thinking (negative thought disorder) and deficits in content with normal volume of words. It is manifested as decrease in verbal communication, increased latency to response, short verbal responses, paucity or complete lack of spontaneous speech and brief, laconic, empty replies. According to DSM 5 alogia is an impoverishment in thinking that is inferred from observing speech and language behavior. There may be brief and concrete replies to questions and restriction in the amount of spontaneous speech (termed poverty of speech). Sometimes the speech is adequate in amount but conveys little information because it is over concrete, over abstract, repetitive or stereotyped (termed poverty of content). [17]

Subdomains of NS

Subsequent to the description of the general categories of NS the two subdomains werereported by Blanchard and Cohen and Kirkpatrick and Fischer in 2006. They are the expressivity domain (blunted affect and alogia) and the experience domain (avolition and anhedonia). The expressivity subdomain has strong correlation with asociality. It is postulated that these two subdomains are possibly connected to two different areas in the brain and have different circuits. [16] But the significance of the two domains has no clear cut reported research evidences to date.

Classification of NS

The NS are classified into different groups: Primary and Secondary, Enduring and Non enduring, Persistent and Non persistent, Deficit and Transitory and Type A and Type B. A working classification for clinical use is offered by Greden and Tandon. [3] According to this classification the NS are classified mainly into the Enduring and the Non enduring symptoms. Both are further classified as Primary and Secondary. Primary Enduring Negative Symptoms (PENS) have been reported to be the core of schizophrenia that would predict poor outcome and treatment failure. They are persistent, stable, non-responsive to drugs and psychosocial methods of treatment, and are responsible for the deficit state. [14,19-21]

The NS were initially classified into Primary and Secondary Negative Symptoms by Carpenter. [12,14] Primary NS are integral aspect of schizophrenia and not caused by other psychopathology or medicines or environmental factors. Primary NS manifest more commonly in the prodromal and residual phases of schizophrenia. They have no significant correlation to positive symptoms, cognitive deficits or the depressive symptoms. They have significant positive correlation with severity, poor outcome and poor response to antipsychotic medication. The secondary NS are on the other hand believed to be caused by antipsychotic adverse effects, depression, demoralization, psychotic process, environmental deprivation and chronic effects of the disorder. The primary/ secondary distinction has been disputed of late because we have no research evidences to support the same. The akinetic extra

pyramidal symptoms and the depressive symptoms both of which are common in schizophrenia could very well be integral aspects of the disorder like the positive and NS rather than the causes for NS. The phenomenological characteristics of primary and secondary NS are one and the same and they are indistinguishable. The distinction is currently made entirely by clinical judgment or statistical computation based on the association with sources of causative factors. [19,20] Persistent Negative Symptoms (PNS)a concept introduced by Buchanan is perhaps better for clinical trials than PENS. [14, 21] The PNS is larger than PENS. It is a broader concept and includes both primary and secondary NS that persist despite treatment. PNS at the same time is less heterogeneous than the general concept of NS. PNS is operationally defined for research in terms of moderate severity, defined threshold of positive symptoms, absence of or low depressive symptoms, absence or low extrapyramidal symptoms and demonstrated clinical stability for an extended period of time prior to trial (for at least 6 months). [21]

Relationships to other Symptoms of Schizophrenia

Schizophrenia is more than psychosis. The positive symptoms (delusions, hallucinations, formal thought disorders and catatonia), the NS, the mood symptoms (depressive symptoms and manic symptoms) and cognitive impairments are all described as symptoms of schizophrenia. The symptoms of schizophrenia are not necessarily unique to schizophrenia. The brain circuits and the neurotransmitter tracts are different for the different dimensions of the clinical manifestations in schizophrenia. [22] The negative, positive, depressive and cognitive symptoms are probably different aspects of schizophrenia. There are overlaps between NS and cognitive and depressive symptoms. Such overlaps could be attributed to the problems related to conceptual clarity and the degree of interference of coexistent other dimensions of symptoms in the accurate assessment and evaluation of the NS. However, the NS have no significant correlation to depressive symptoms or cognitive impairments. The NS have no definite relationship with positive symptoms. Among the positive symptoms formal thought disorders are reported to have the best relation to NS. However the negative and positive symptoms are reported to co-vary particularly in the active phase of schizophrenia. In general the NS have no significant correlation to the cognitive impairment. Cross-sectional correlation between NS and cognitive impairment is not statistically insignificant [3,5-7,15,22-27] But there are reports regarding significant correlation of NS to cognitive impairment in some of the longitudinal investigations [23,25,26] Being the core dimensions of schizophrenia the relationship between NS and cognitive deficits is of immense importance. Four theoretical models are proposed to understand the relationship between them. [26] First model indicates that NS and cognitive deficits are overlapping single dimension of symptoms produced by same etiology (one etiology produces negative cognitive dimension). According to second model same etiology produces the two distinct dimensions of symptoms (one etiology produces negative dimension and cognitive dimension of symptoms). According to the third model there are two separable but related etiologies each one of them causing two related but distinct dimensions of symptoms(etiology one produces both dimensions and another related second etiology also produces both dimensions of symptoms). Fourth model indicates that NS and positive symptoms are independent dimensions but are related either due to overlapping measurements or definition or due to shared correlation with distal measures(etiology one and etiology two produces overlapping but distinct negative and cognitive dimensions of symptoms). German investigators do not tend to agree that the so called ‘basic symptoms’ are synonymous to’ NS’. It has been reported that the ‘basic symptoms’ are

in fact the core of schizophrenia and they manifest subsequently as NS and cognitive symptoms.

The validity of the concept of NS is not well established. Blanchard and Cohen examined the structural validity of NS in terms of whether NS represent a domain separate from other symptoms of schizophrenia and whether there are structural multiple dimensions within the NS. In their review of exploratory and confirmatory factor analytic studies the authors report that the NS appear to consistently emerge as separate from positive symptoms, affective symptoms and symptoms of disorganization. Factor analytic studies suggest that the NS construct is multidimensional; involving at least two dimensions (diminished expression and anhedonia-asociality). The later suggestion is not conclusive in view of the serious limitations of the studies reviewed. [28]

NS and Phases of Schizophrenia

Although considered the hallmarks of chronic state, the NS as a matter of fact are manifest in all phases of schizophrenia. [3,6,7,12,15,27,29] In the prodromal phase the NS characteristically occur along with pre-psychotic behaviour and social role deficits. They are present in the early phase of schizophrenia along with or without positive symptoms. During the active phase of schizophrenia they apparently tend to co-vary especially with treatment related remission and relapse. The NS are more likely to become more prominent in the later phase of the disorder after remission of the positive symptoms. NS are likely to persist and to provide the substrate upon which socio occupational deterioration develop and progress. [3,12,15, 23, 24, 27] The prevalence of NS reported in the prodromal stage is as high as 73%. NS is reported to occur in 15% during the first episode of schizophrenia and 25 – 30% in patients with chronic schizophrenia. During residual phase 75 % of patients with schizophrenia have manifest avolition and apathy and 71% have anhedonia-asociality. [3,5-7,15, 23,24]

ASSESSMENTOF NS

Although the NS are the core features or the fundamental symptoms of schizophrenia they are not well defined and unambiguous. They are difficult to be measured properly. But due to the increasing interest in the NS and related dichotomy of schizophrenia, a good number of scales are proposed to rate and identify the NS. Today we have a reasonably large list of assessment tools for NS with different definitions, methods and concepts (Table-I). [1-3,5-7,15,29] There are two broad categories of rating scales, the scales which are not specific for NS assessment and the scales which are specific. There are various basic problems in the assessment of the NS. First of all the NS represent the absence of behaviour or function and we have to rate the 'absence'. We do not have the exact agreement on the components of the NS. The relative importance assigned to each component of the NS remains ill defined. We require multiple sources of information for rating NS. All these problems are compounded by the ambiguity and the uncertain validity of the concept. The complexity of the concept calls for operational definitions. Before the introduction of the specific scales for NS, the non-specific scales such as Wing's Rating Scale, Manchester Scale, BPRS and CPRS were used in research. The non-specific scales are sensitive to change. Currently SANS, PANS and SDS are the most widely used scales for NS. [3,6,7,9,11-13] The specific scales have relative similarities, differences and distinctions. The NS are better defined in the specific scales. By and large their reliability and internal consistency are established. But their validity remains uncertain. The specific scales for NS are not sensitive to change although they are extensively used for RCTs. To overcome some of the shortcomings of the commonly used scales three new generation scales for assessment of NS are introduced recently (NSA-4, BNS and CAINS). [30-34]

TABLE-I. SCALES FOR ASSESSMENT OF NEGATIVE SYMPTOMS		
Name of Scales	**Authors**	**Year**
Non Specific Rating Scales		
Wing Rating Scale (WRS)	Wing et al	1961
Brief Psychiatric Rating Scale (BPRS)	Overall and Gorham	1962
Krawiecka Manchester Scale (KMS)	Krawieka et al	1977
Comprehensive Psychopathology Rating Scale (CPRS)	Asberg et al	1978
Schedule for Affective Disorders and Schizophrenia. SADS.	Endicott and Spitzer	1978
Specific Subjective Rating Scal		
Subjective Deficit Syndrome Scale (SDSS)	Petho and Bitter	1985
Subjective Experience of Deficit Scale (SEDS)	Liddle and Barnes	1988
Specific Objective Rating Scales		
Scale for Emotional Blunting (SEB)	Abrams and Taylor	1978
Scale for Assessment for Negative Symptoms (SANS)	Andreasen. NC.	1981
Negative Symptom Scale- LFM. (NSS-LFM)	Lewine, Fogg& Meltzer	1983
Negative Symptom Scale- PGH. (NSS-PGH)	Pogue-Geile& Harrow	1984
Negative Symptom Rating Scale (NSRS)	Iager et al	1985
Bonn Scale for Assessment of Basic symptoms (BSABS)	Gross et al	1987
Positive And Negative Symptom Scale (PANSS)	Kay et al	1987
Schedule for Deficit Syndrome (SDS)	Carpenter et al	1988
Negative Symptom Assessment Scale (NSA-26)	Alphs et al	1989
Negative Symptom Assessment Scale (NSA-16).	Axelrod etal	1993
Motor Affective Social Scale (MASS)	Tremeau et al	2008
Brief Negative Symptom Scale (BNSS)	Kirkpatrick et al	2010
Negative Symptom Assessment Scale (NSA-4)	Alphs et al	2011
Clinical Assessment Interview for NS (CAINS)	Blanchard J J et al	2011

The authors hold the view that the NIMH MATRICS Consensus Statement on NS highlights the current concepts about NS. [25] Briefly the following are the areas of agreement among the experts.

1. NS constitute a distinct therapeutic indication area in schizophrenia.
2. NS and cognitive impairment represent different domain. The areas of interaction and overlap could be defined in future. Current documented available data indicate substantial distinction between NS and cognitive impairment in schizophrenia.
3. NS have face validity as disorder manifestations and they represent loss or diminution of normal functions.
4. The domains of NS include blunted affect, alogia, asociality, anhedonia, and avolition. There are substantial correlations across these domains, but they may have separate neurobiological substrates and may represent separate therapeutic targets. The structure of relationships among these domains and their predictive validity require further study.
5. Distinction between primary and secondary NS is not essential for research on treatment for NS in schizophrenia.
6. *Structure of the Scale for the Assessment of NS (SANS) is preferred to that of the Positive and Negative Syndrome Scale(PANS). However, the PANS, SANS, and perhaps other assessment approaches are appropriate for application in current clinical trials.*
7. Persistent and clinically significant NS are an unmet therapeutic need for a large proportion of patients with schizophrenia.
8. Within NS definition of a clinically meaningful effect size needs further review.
9. Length of clinical trial will vary with the purpose of the trial. Proof of concept study may be brief. The preliminary efficacy studies may be 4-6 weeks. Registration studies are likely to be substantially longer (in the range of 6 months) in order to document persistent efficacy.
10. Paradigmatic design for clinical trials of persistent NS would include clinically stable patients whose NS persist with adequate antipsychotic drug treatment. This would be a double-blind, placebo-controlled comparison of parallel groups, in which the putative NS treatment is administered as a co-medication with a second-generation

antipsychotic.

11. Paradigmatic design for a co-administered drug is less satisfactory when testing a broad spectrum antipsychotic agent, that is, one that may have superior efficacy for both positive and NS.

The experts also agreed on the following recommendations. The development of a new instrument that includes the five agreed-upon domains would advance work in this area. Such an instrument needs to be applicable in both in-patient and outpatient clinical trials and needs to be sensitive to change. There is need to establish a framework to promote the identification and testing of drugs for a NS indication. It is likely that this process would be similar to the MATRICS process for drug discovery for the treatment of cognitive impairment in schizophrenia. [25]

CLINICAL IMPORTANCE

The NS have clinical importance in the diagnosis, prognosis and treatment of schizophrenia as well as in understanding the biology of schizophrenia. The presence of NS and their importance in other psychiatric disorders like depressive disorder, bipolar disorder and schizotypal disorder are recognized.

Diagnosis of Schizophrenia

The NS are not pathognomonic of schizophrenia and are not exclusive to schizophrenia. They are reported to be present in other disorders and states. They are manifest in other psychiatric disorders, medical disorders and other conditions. [15,24,27,35,36] NS are reported to occur in Schizophrenia, Depressive Disorder, Organic Mental Disorders(Dementia), Anxiety disorders(Obsessive Compulsive Disorder), Schizotypal Disorder, Personality Disorder (Schizoid and Anankastic PD), Bipolar Mood Disorder, Schizoaffective Disorder, Neuroleptic Induced Deficit Syndrome, Parkinson's Disease, Basal Ganglia Diseases, Frontal Lobe Syndromes, Diabetes Mellitus, Prisoners, Institutionalization and in Healthy Individuals. Pervasive avolition, affective blunting and alogia are significantly more common in schizophrenia and they are most characteristic of the disorder. We have reported from India that the NS are integral part of schizophrenia and that they are independent of the environment and medical and psychosocial treatment received by the patient. [6,7] We have also reported that the NS in SANS could not distinguish schizophrenia from depressive disorder. It is recently reported that the finer aspects of the phenomena of anhedonia, avolition and asociality and subjective awareness of NS are possibly different in schizophrenia and major depressive episodes. [18,36-39]

The diagnostic potential of NS is recognized and the major current diagnostic systems include them in their criteria for diagnosis of schizophrenia. [3,40] In both ICD-10 and DSM 5 the NS are given importance. They are included under characteristic symptoms for diagnosis. The NS when manifest alone is insufficient to make a diagnosis of schizophrenia. They are not necessary to make a diagnosis. In ICD-10 the NS belong to one of the nine groups of characteristic symptoms of schizophrenia. They do not belong to the first four groups that are given most significance for diagnosis of schizophrenia. In DSM 5 the NS are one among the five groups of characteristic symptoms of schizophrenia. They are not among the most significant symptoms for diagnosis. DSM IV TR included alternative dimensional models of schizophrenia (negative dimension) under criteria sets and axes provided for further study. Such dimensional models are discarded in DSM 5 due to lack of research evidences. [17] Whether NS are given the due importance that they deserve in the diagnosis of schizophrenia in ICD 10 and DSM 5 is an arguable issue. [40] On the contrary anhedonia is given due importance in the diagnosis of depressive disorders in ICD-10 and DSM 5.

Prognosis of Schizophrenia

Clinical experience and research evidences suggest that the NS are by and

large associated with socio occupational deterioration and interpersonal deficits. The NS are accepted as one of the predictors of poor prognosis in schizophrenia. Although research data is insufficient to draw definite conclusions due to methodological limitations, it is universally accepted in clinical practice that persistent/ primary enduring NS carry poor outcome. It is reported that the PENS and PNS do not respond to treatment and indicate poor outcome whereas the other NS have at least modest response to Clozapine/ SGA, therefore need not necessarily indicate poor prognosis. [2-7,12,14,15,21,29] The NS have significant correlation with treatment resistance, poor quality of life, poor subjective well-being and interpersonal deficits. There are reports that they have strong association with persistent cognitive deficits and that the NS provoke more expressed emotions.

Treatment of Schizophrenia

Parallel to the introduction of second generation antipsychotics in 1990s, there have been several important changes in conceptualization of schizophrenia. First of all, the concept of schizophrenia transitioned from a disorder defined by psychosis to one with multiple symptom domains. The NS, the mood symptoms and the cognitive symptoms are recognized as integral manifestations of the disorder. Secondly, discussions and debates on functional versus clinical recovery paved way to the inclusion of functional recovery in the definition of outcome in schizophrenia. Thirdly, early evidences indicated that SGAs, with their different mechanisms of actions, could effectively treat all the domains of manifestations. [22,23, 41-46] NS are more difficult to treat than the positive symptoms of schizophrenia and represent an unmet therapeutic need for large number of patients with schizophrenia. [22,23,25,41-46] While antipsychotic medications to treat the symptoms of schizophrenia have been around for six decades, they have done little to address the significant functional impairments in the disorder that are associated with NS. [41,46] With over 25 years of clinical experience involving SGA, there have been further setbacks in our thinking. Initial enthusiasm regarding the clinical benefits of SGAs over FGAs for symptoms beyond psychosis has been eroded considerably based on accumulated research data. Concurrently, the relevance of both negative and cognitive symptoms in terms of functional recovery has become central to the concept of measurements of outcome and hence in establishing effective treatments in schizophrenia. [22,41,46] Existing pharmacological options may be effective in treating secondary causes of NS, such as antipsychotic side effects and depression. Pharmacotherapy and psychosocial treatments are being developed and tested in TRS patients with PNS as their primary targets. [22,23, 41, 43, 45,46]

The treatment approach in schizophrenia with prominent NS, with and without positive and other domain symptoms are different. Other than the FDA approved indications of clozapine in schizophrenia, prominent PENS/PNS is a clinical indication for clozapine treatment. However, there are no currently FDA approved treatments for severe and persistent NS (PNS) that are not responsive to treatments for secondary causes. The treatment methods are based on the different assumptions about the probable causes of NS. But despite such conspicuous limitations we have several therapeutic techniques that could be put together in an effective treatment program. The secondary NS by and large respond to treatment. Primary non enduring NS respond to SGAs where as the primary enduring NS/ persistent NS has poor response. [22,23,41,45,46] The SGAs, other drugs acting through the cholinergic, adrenergic, serotonin and other neurotransmitter systems along with cognitive, occupational and social rehabilitation procedures offer promising rational approach towards treatment of the NS in schizophrenia. Clinical experience is in favour of reduction/ replacement/ avoidance of FGAs. The first line medicines

advocated to treat NS are SDA/DPA. Clozapine, Amisulpride and Levosulpiride are second line drugs. Other drugs used to augment efficacy include a different class of SDA, SSRI, NRI, Modafinil and NMDA Antagonists. Research evidences indicate that the treatment at best has only modest effectiveness on the PNS and clozapine is perhaps the most effective available medicine. Other medicines used to treat NS have uncertain efficacy. [15, 22, 23, 27,41,44-46]

A large variety of drugs have been investigated for their efficacy and effectiveness in schizophrenia with NS that include antipsychotics, antidepressants, CNS stimulants, anticonvulsants, drugs related to NMDA, Serotonin and Cholinergic receptors, Neurosteroids, Sex Hormones, Oxytocin, anti-inflammatory drugs and others(Table-II). The notion that pharmacological treatment could favorably influences NS originated from reports about the unique effectiveness of clozapine amongst antipsychotics in treatment-resistant schizophrenia. Clozapine and other SGAs including Olanzapine, Risperidone, Quetiapine, Amisulpride, Ziprasidone and Lurasidone are used to treat NS in schizophrenia. Several recent meta-analyses report that the newer antipsychotics are not superior to their conventional counterparts in the treatment of NS and that the effect in either case is modest. [41,46-48]

There are several reports on the efficacy of antidepressants in the treatment of NS in schizophrenia. Most recent meta-analysis reports that antidepressants have some beneficial effects on NS that differ between agents and that the evidence is not strong enough to support their clinical use. Two earlier meta-analyses provide equivocal evidence and a lack of support for antidepressant use. Bupropion fails to demonstrate efficacy but Reboxetine and Mirtazapine are found to have efficacy on NS. But in such clinical trials the NS is not the primary target. [41,46,49,50]

Reports on clinical trials on efficacy of methylphenidate, *d*-Amphetamine, Modafinil, Armodafinil and Lisdexamfetamine (LDX) used as augmenters are in literature. A recent meta-analysis reports efficacy of Modafinil and Armodafinil in the treatment of NS, but the effect size is small. Early reports suggest that LDX may improve NS. [41,46,51] There are no specific research reports in favor of efficacy of anticonvulsants in NS in schizophrenia although they are frequently used to augment the antipsychotics. [41, 46]

Despite equivocal clinical evidence there has been lot of clinical trials on the efficacy of glutamate targeted drugs in the treatment of NS. Numerous compounds, involving both ionotropic and metabotropic receptors, have been evaluated over the last two decades. Two meta-analyses, not specific to NS, suggest favorable, but small size efficacy of drugs enhancing NMDA receptor activity such as *d*-Serine, Sarcosine, *N*-Acetyl-cysteine, and D-Cycloserine. Other compounds targeted at NMDA receptors through other mechanisms have been investigated. Notable among them are GlyT1 Inhibitor (Glycine Transporter 1 Inhibitor -Bitopertin), mGluR2/3-positive allosteric modulator (LY2140023) and NMDA receptor antagonists (Amantadine and Memantine). Despite the initial enthusiasm, disappointing recent results with Bitopertin and LY2140023 have led to their discontinuation for this indication. A meta-analysis examining Amantadine and Memantine does not support the utility of these medications in the treatment of NS, although the focus is not on NS specifically. An RCT published subsequently and looking at NS as the primary outcome reports that Memantine is effective in improvement of NS with a large effect size. [41,46,52,53]

A meta-analysis evaluating cholinesterase inhibitors in schizophrenia (Rivastigmine, Donepezil, Galantamine) reports improvement in selected measures of cognition, but not NS. Another meta-analysis evaluating drugs targeted glutamatergic, serotonergic and cholinergic receptors does not report effect on NS with

Donepezil, and Galantamine. But a Cochrane review around the same time, and specific to cholinesterase inhibitors in schizophrenia, indicates a signal for improvement of NS. The authors could not come across any RCTs involving a cholinesterase inhibitor where NS are the primary outcome. [41,45,46,54]

A number of newer α7 nicotinic acetylcholine receptor (α7 nAChR) agonists/partial agonists as well as positive allosteric modulators are investigated for their efficacy on NS in schizophrenia. CDP-Choline, α7 nAChR agonist TC-5619 and EVP-6124 are examples of such drugs. [41,45,46] Selective 5-HT_2 antagonists (Ritanserin) and selective 5-HT_3 antagonists (Ondansetron, Tropisetron, Granisetron) are investigated for efficacy specifically on NS in schizophrenia. Neurosteroids (DHEA, Pregnenolone, l-Theanine), adrenal hormones involved in the production of androgens and estrogens, Raloxifene (estrogen receptor modulator) and oxytocin are investigated for their efficacy on NS in schizophrenia. The neurosteroids and oxytocin have evidences in favor of their efficacy in some of the clinical trials. [45,46] Minocycline, a broad-spectrum tetracycline antibiotic with neuroprotective properties mediated through anti-inflammatory, anti-apoptotic, and antioxidant effects has received the greatest attention. A recent meta-analysis supports its value in the treatment of NS, although this domain is not the primary outcome. ASA, Cox-2 inhibitors, Dextromethorphan, Methotre-xate, Interferon-y, Atorvastatin, Pravastatin and Pioglitazone are under investigation for their efficacy on NS in schizophrenia. Based on current available research data the most promising drugs for NS are the Neurosteroids (Pregnenolone), NMDA receptor targeted drugs (d-serine and Memantine) Glycine transporter-1 inhibitors, α7-Nicotinic receptor targeted drugs, Oxytocin and Anti-inflammatory drugs (Minocycline). [41,45,46]

TABLE-II. LIST OF DRUGS AND OTHER TREATMENTS EVALUATED

1.	FGA: Loxapine, Molindone, Sulpiride, Pimozide, Fluspireline, Penfluridol, Flupenthixol
2.	Clozapine.
3.	SDA: Risperidone, Olanzapine, Amisulpride, Aripiprazole, Quetiapine, Ziprasidone, Lurazidone, Bonanserine, Zoptepine.
4.	Antidepressants: SSRI. MAOI. Bupropion. Reboxetine. Mirtazapine.
5.	CNS Stimulants: Methylphenidate. d-Amphetamine. Modafinil. Armodafinil. LDX
6.	Anticonvulsants: Divalproate. Carbamazepine. Oxcarbazepine.
7.	NMDA /Glutamate Targeted Drugs: D-Serine. Sarcosine. N-Acetyl-Cysteine. D-cycloserine. Bitupertin. LY21 40023. Memantine. Amantadine. Lamotrigine. Rituzole, AMPA Kines.
8.	Cholinesterase Inhibitors. [Donepezil. Galantamine. Rivastigmine.
9.	Nicotine Receptor (Alpha 7 nAChR) Targeted Drugs: CDP- Choline. TC 5619. EVP 6124 Anabaseine.
10.	Serotonin Receptor Targeted Drugs: Ritanserin (S2). Ondansetron. Tropisetron. Granisetron (S3) Lecozatan. Buspirone. Tandospirone. Gepirone. Vilazodone. Epivanserin. Agomelatin. Vibicaserin.
11.	Neurosteroids: DHEA. Pregnenolone. l-theanine.
12.	Hormones: Raloxifene. Oxytocin.
13.	Anti-inflammatory Drugs: Minocyline. ASA. Cox-2 Inhibitors.
14.	Drugs Targeted on Cannabinoid Receptors: Rimonabant, AVE 1625.
15.	Newer Drugs Targeted at Dopamine Receptors:Bifeprunox. Sarzotzn. Nemonapride. Fananserin.
16.	COMT Inhibitors:Tolcapone. Nitecapone.
17.	Drugs targeted at Peptide Receptors:Neurokinin (NK3 --Talnetant, Osnetant.). Neurotensin. CCK. Cytokines.
18.	Free Radical Scavengers: Vitamin E, Lazaroids.
19.	Drugs Targeted at Sigma-1 Receptors: BMY 14802. OPC-1.
20.	Other Drugs: Dextromethorphan. Methotrexate. Interferon Y. Atorvastatin. Parvastatin. Pioglitazone.
21.	Prodromal Schizophrenia Treatment with multiple drugs.
22.	Multiple Drug Treatment: (APP + Augmenters).
23.	Brain Stimulation: TMS. TCS. VNS. ECT. DBS.
24.	Psychosocial Methods: Environmental Enhancement. Skill Training. Cognitive Remediation Therapy. Nidotherapy. CBT.

Brain stimulation is another line of investigation that currently generates considerable interest on NS in schizophrenia. Transcranial Magnetic Stimulation, Transdirect Current Stimulation, ECT, Vagal Nerve Stimulation and Deep Brain Stimulation are investigated to evaluate their efficacy on NS in schizophrenia. There are no reports indicating their probable benefits on NS but there are no conclusive evidences for their efficacy. [41] There are research reports

about the feasibility and effectiveness of psychosocial methods of treatment as adjuncts to medical treatment for NS in schizophrenia. The effectiveness of long term psychosocial treatment may correspond to the favorable neuroplastic changes in brain. [22,23,41,55,56]

Biology of Schizophrenia

The progress in the understanding of NS and their importance in schizophrenia challenged the then existent frontiers and concepts of schizophrenia. [3,22,23,57] Parallel to this advance in the knowledge of NS, the unique effectiveness of Clozapine in TRS and the introduction of the SGA contributed to the modifications in the conceptualization of schizophrenia. We arrived at the realization that schizophrenia is more than psychosis. Essentially there has been a transition in the concept from a disorderdefined by psychosis to a heterogeneous one with multiple symptom domains and delicately defined frontiers with uncertain limits and boundaries.The research on NS has contributed much towards better understanding of the biology of schizophrenia. It is clear now that single receptor dysfunction, single pathology, single marker or single etiology will not explain the complex process and pathophysiology of schizophrenia. Research evidences on NS generated different clinical and etiological models of schizophrenia with different biological and neurological explanations. [3,23,57-60]

New Clinical Models of Schizophrenia New clinical models of schizophrenia defined essentially in terms NS came in to existence in clinical practice and research. They are Type 2 Schizophrenia (Crow, 1980), Negative Schizophrenia (Andreasen, 1982), Deficit Schizophrenia (Carpenter, 1988), Residual Schizophrenia (ICD-10, DSM III to DSM IV TR), Negative (Deficit) Dimension (DSM IV TR). [1,4,12-14,57-60] Unlike the classical subtypes of schizophrenia the new clinical models are supported by more research evidences in favor of substantial validity. Such evidences include structural and functional brain imaging, neurophysiological, neurochemical, neuroendocrine and neurocognitive data. Although not substantial, there are significant differences in research data in substantial number of schizophrenia patients with NS and positive symptoms. For example the structural brain abnormalities (developmental/ degenerative) are more in Type 2, Negative, Deficit and Residual Schizophrenia in comparison to their counterparts. Several other data including neurophysiological, cognitive, endocrine and neurological biomarkers are significantly different in the new clinical models of schizophrenia. [1,4,12-14,23,57-61]

New Neurotransmitter Pathways Results of investigations on the NS implicate new neurotransmitters and pathways as explanations for the symptoms. [3,22,23,52,57,58,61,62] The dopamine hypothesis is modified to includeprefrontal cortex dopamine deficiency (DLPFC D1) in addition to subcortical dopamine excess (LS, BG, D2).Cholinergic hyperactivity in limbic system is reported to be related to NS and cholinergic hypoactivity to PS. The fluctuation in the limbic and prefrontal cholinergic and dopaminergic balance is reported to be one of the reasons for the wide variations in the symptoms of schizophrenia. State dependent norepinephrine dysregulation is associated with NS and PS. Norepinephrine excess is associated with NS in prodrome and both negative and positive symptoms in active phase. Norepinephrine deficiency is associated with NS in the residual phase. The secondary NS due to D2 receptor antagonists are associated with norepinephrine deficiency. Norepinephrine system is essential for D1 and D2 receptor sensitivity. The state dependent norepinephrine dysregulation is perhaps another reason for clinical heterogeneity in schizophrenia. Serotonin (5HT1 & 5HT2) receptor activity deficiency is reported to have significant association to NS and cortical atrophy in patients with

schizophrenia. Excess GABA and deficient dopamine receptor activity have significant association to prominent NS and low GABA and high dopamine activity is associated with prominent positive symptoms. Both hyperglutamateric state leading to excitotoxicity and neuronal loss, and hypoglutamatergic state are associated with NS.

Brain Areas and Circuits

Ventromedial PFC and the Ventral Anterior Cingulate Cortex are the brain areas associated with NS in schizophrenia. The cortico- striato- thalamo- cortical circuits (CSTC) from the ventromedial prefrontal cortex(VMPFC) is reported to be involved in the manifestation of NS. The mesocortical dopamine pathway to VMPFC (MC DA Pathway), the mesolimbic dopamine pathway(ML DA Pathway) through the reward system, the cortico brainstem glutamate pathway(CBS GLU Pathway), corticostriatothalamo cortical glutamate pathway (CSTC GLU Pathway) and the serotonin pathways(5HT1, 5HT2) modulating the dopamine and glutamate pathways are implicated in pathophysiology of negative schizophrenia /deficit schizophrenia. [3, 61,62]

Neuroendocrine changes

Neuroendocrine changes differ in schizophrenia depending on predominance of negative or positive symptoms. GH response to TRH is increased in NS implicating the cholinergic activity. GH response to apomorphine, clonidine, hypoglycemia and sleep is reduced implicating dopamine and norepinephrine systems. DST non- suppression is seen in NS with venticulomegaly. Increase in vasopressin is implicated in NS in deficit state. Reduced CCK in hippocampus and increased substance P also has been found in NS. Others like VIP, Somatostatin, Opioids, Neurotensin and Bombesin, Prolactin, FSH and LH have also been implicated in NS. These neuroendocrine alterations in NS indicate complex involvement of multiple neurotransmitters in schizophrenia. [3,22,23,57,61,62]

Brain Structure, Function and Neuropathology

Structural and functional brain images in schizophrenia indicate ventricular dilatation (fourth and third ventricles),global and regional cortical atrophy(FL TL LS BG), global and regional grey matter density loss (PFL), reduction and enlargement of specific brain regions and structures (hippocampus, temporal lobe, frontal cortex, corpus callosum, amygdala, para hippocampal region, hypothalamus, medial temporal areas, anterior cingulate cortex and caudate nucleus) white matter structural and functional changes, global and regional metabolic and molecular alterations in functions in schizophrenia [61-64] The neuropathological studies reveal primary or secondary brain cell damage such as definite brain atrophy, dysmorphism and gliosis, which are diffuse but with focal predominance in the above regions in the brain. The structural and neuropathological abnormalities are more severe and more common in negative schizophrenia/ deficit schizophrenia. [3,57,61,62]

Etiological Models of Schizophrenia

All the accepted models of etiology of schizophrenia are supported by and explained by the NS. The genetic model, the neuro developmental model, the degenerative model and immunological model are supported by the NS. The negative schizophrenia/ deficit schizophrenia is more genetic, more developmental and more degenerative than the positive schizophrenia. [3,57,61,62]

NEGATIVE SYMPTOMS IN OTHER PSYCHIATRIC DISORDERS

NS are reported and investigated in Depressive Disorder, Bipolar Mood Disorder and Schizotypal Disorder. [6,18,35,36,65-70] Recent reports suggest that primary NS (anhedonia, affective blunting and avolition) could be core features of MDD and they have significant correlation to cognitive deficits and structural and functional changes in the brain. [69] Qualitative finer distinction of the NS in depressive disorder and schizophrenia is an

area of current research. [18,69] Based on NS schizotypal disorder can be classified into positive and negative subtypes. [70]

CONCLUSIONS

NS in psychiatry are deficits in experience and behavior that are attributed to loss of functions of brain. NS have been conceptualized as the core aspect of schizophrenia. The other probable core domain is cognitive deficits. Strauss, Carpenter and colleagues reintroduced NS to psychiatry in 1974. The current concept is descriptive, not based on any theory and does not imply neurobiology or relationship to other symptoms. The NS concept in psychiatry is more Reynoldian than Jacksonian.

The five general categories of NS include avolition, anhedonia, affective blunting, alogia and asociality. The subdomains of NS are experience domain (avolition and anhedonia) and expressivity domain (affective blunting and alogia). The NS are initially classified into primary and secondary NS (Carpenter). Primary Enduring NS (PENS) have been reported to be the core of schizophrenia that would predict poor outcome and treatment failure. . The importance of primary versus secondary NS distinction has been currently disputed in the light of absence of research evidences to support the same. The Persistent NS (PNS-Buchanan) is perhaps better for clinical trials than the PENS. The NS have no definite relationship with positive symptoms.There are overlaps between NS and cognitive and depressive symptoms. Such overlaps could be attributed to the problems related to conceptual clarity and the degree of interference of coexistent other dimensions of symptoms in the accurate assessment and evaluation of the NS. However, the NS have no significant correlation to depressive symptoms or cognitive deficits. Though the NS have adequate reliability the validity of the concept of NS is not well established. Although considered as the hallmarks of chronic state in clinical practice, the NS as a matter of fact are manifest in all phases of schizophrenia. The available nonspecific and specific scales for assessment of NS have certain unique merits and significant demerits (Wing, Crow, Andreasen, Kay). The new generation assessment instruments BNS and CAINS are likely to give more reliable and valid data that are more sensitive to change (Kirkpatrick, Blanchard). The 'NIMH MATRICS Consensus Statement on NS' highlights most of the current concepts about NS.

Clinical significance of NS in terms of diagnosis, prognosis and treatment options in schizophrenia has been recognized. The NS are not diagnostic of schizophrenia and are not exclusive to schizophrenia. They are manifest in other psychiatric disorders, medical disorders and other conditions. Finer qualitative aspects of NS and subjective awareness and concern for NS are possibly different in schizophrenia and major depressive episodes. Substantial research evidences support the clinical realization that prominent NS particularly PNS/PENS indicate poor outcome and quality of life in schizophrenia. The available pharmacological options fail to be effective in schizophrenia patients with prominent PNS/PENS. Several recent meta-analyses report that the newer antipsychotics including clozapine are not superior to their conventional counterparts in the treatment of NS and that the effect with clozapine is at best only modest. Researchers are investigating drugs that act on new sets of receptors. Based on current available research data the most promising drugs for NS are the neurosteroids (pregnenolone), NMDA receptor targeted drugs(d-serine and memantine) glycine transporter-1 inhibitors, α7-nicotinic receptor targeted drugs, oxytocin and anti-inflammatory drugs (minocycline). The concept of NS brought about substantial modifications in our understanding of neurobiology of schizophrenia and etiological and clinical models of schizophrenia. NS are related to brain damage in schizophrenia due to

genetically determined compromised quality, developmental assault and degenerative process.

Management of PNS/PENS represents a significant unmet need in psychiatry. Improvements in definition, characterization, assessment instruments and unique RCT models are needed in order to promote research aimed at developing effective interventions. The existing knowledge on NS is limited. Future research should focus on new options for treatment, basic symptoms and their relation to NS as well as subdomains of NS and their relations to brain areas and circuits. Genes, synapses and neuronal connectivity and their relations to NS will be specific areas of further investigations.

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