

# Evaluation of Assemblage and Manageability of Negative Symptoms of Schizophrenia: A New Stance

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## Abstract

**Background:** Negative symptoms of schizophrenia are categorized by some of the scholars into 'primary vs. secondary', 'enduring vs. transitory' and 'treatment-resistant vs. treatment-responsive' groups. But it looks that such kind of assembling may not be basically reasonable.

**Objective:** Exploring the authenticity of the aforementioned grouping, and reports concerning resistance of negative symptoms against current managements.

**Method:** In three serial double-blind clinical trials, the effectiveness of different augmentative medications regarding improvement of negative symptoms had been evaluated. Scale for Assessment of Negative Symptoms was the primary outcome measure.

**Results:** Citalopram, alprazolam, and clomipramine in the first evaluation, nortriptyline in the second study, and maprotiline in the third trial were meaningfully more effective than placebo. In general, 31.2%, 28%, 26.4%, 24% and 22.4% of patients experienced some improvement (around 20%) in the severity of 'attention deficit', 'alogia', 'affective blunting', 'anhedonia- sociality' and 'avolition-apathy', respectively.

**Conclusion:** As said by the outcomes of the current study, classification of negative symptoms into 'primary vs. secondary', 'enduring vs. transitory' and 'treatment-resistant vs. treatment-responsive', may not be essentially defensible. Moreover, negative outlook concerning inflexibility of 'primary negative symptoms', against existing therapeutic methods demands renovation.

**Keywords:** Schizophrenia; Deficit Syndrome; Primary Negative Symptoms; Secondary Negative Symptoms; Treatment-Resistant

## Introduction

Direct and indirect health costs of schizophrenia in England in 2004-5 were £6.7 billion and it is in the top 10 causes of worldwide disability [1]. In patients who progress to chronic schizophrenia, the acute symptoms usually resolve (with or without treatment) and the characteristic picture becomes one of a 'burnt out' disease, which is called deficit syndrome with predominant negative symptoms. On the other hand, the positive-acute/negative-chronic distinction is not outright. Positive symptoms regularly persist or re-emerge in chronic cases, and some patients have negative symptoms in their first episode [2]. According to DSM-5 and for diagnosis of schizophrenia: "... two Criterion A symptoms, as a minimum, should be existent during a one-month period or longer [3]. While grossly disorganized or catatonic behavior (Criterion A4) and negative symptoms (Criterion A5) may also be present, one of these symptoms, at least, should include the obvious presence of delusions (Criterion A1), hallucinations (Criterion A2), or disorganized speech (Criterion A3) (p.99).

In addition, Schizophrenia involves impairment in one or more main areas of functioning (Criterion B). Negative symptoms are common in the prodromal and residual stages and can be severe. Persons who had been generally active may become withdrawn from their former routine schedules. Such manners are often the initial sign of a malady...." "... While negative symptoms account for a considerable portion of the illness linked with schizophrenia, they are less prominent in other psychotic syndromes (p.88). Two negative symptoms are principally noticeable in schizophrenia: avolition and reduced emotional expression. Avolition is a reduction in interested self-initiated determined accomplishments. The patient may be seated for long periods of time and

display slight attention in taking part in occupational or societal actions. Reduced emotional expression as well includes decreases in the manifestation of emotions in the face, eye contact, intonation of speech (prosody), and actions of the head, face and hand that typically give an expressive accent to dialogue.

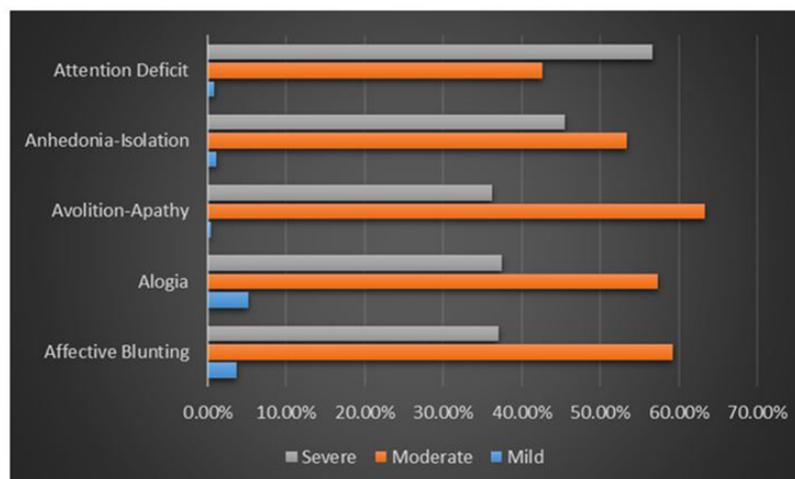
Other negative symptoms include anhedonia, asociality and alogia. Anhedonia is the reduced capability to experience pleasure from encouraging provocations or degradation in the remembrance of previously pleasurable experiences. Asociality mentions to the obvious absence of attentiveness in societal communications and may be related with avolition, but it can likewise be an expression of restricted chances for public connections. Alogia is demonstrated by lessened speech output.....” [3]. In a number of well-known assessment measures, like Scale for Assessment of Negative Symptoms (SANS), ‘attention deficit’ was as well labeled as negative symptom [4]. Moreover, for some scholars and as a research diagnostic criterion, existence of at least two of the abovementioned symptoms for at least twelve months was sufficient for classification of schizophrenia as deficit syndrome or subtype [4]. Mental retardation, depression, anxiety, suspiciousness, drug induced parkinsonism, active positive symptoms (like delusion and hallucination) and lack of environmental stimulants and so on are regarded as potential factors that can reinforce ‘primary negative symptoms’, or produce ‘secondary negative symptoms’.

Among them ‘Affective Blunting’, ‘Alogia’ and ‘Attention Deficit’ are grouped by some of the researchers as ‘enduring’, ‘deficit’, ‘persistent’, ‘trait’ and ‘treatment-resistant’ group and ‘Anhedonia’, ‘Asociality’, ‘Avolition’ and ‘Apathy’ as ‘non-enduring’, ‘phasic’, ‘transitory’, ‘state’ and ‘treatment-responsive’ group of negative symptoms [5]. Hence, it is supposed that the first group is due to structural and developmental factors and the second group is caused by imbalance of dopamine in the mesolimbic-mesocortical circuit [6]. In addition, the first group is usually more evident in the residual or premorbid phase of schizophrenia, while the second group is more observable in the acute (psychotic) phase and pre and/or post psychotic stage. The first group, too, is known by some as poor prognostic sign, while the second group is acknowledged as an indication of good prognosis or as signs that does not have anything to do with prognosis.

Moreover, the enduring group seems to be more prevalent among the patient’s relatives in comparing with the nonenduring group. Even among the enduring cluster, some researchers believe that affective blunting or flattening and poverty of speech, perhaps, are more appropriate for including as ‘primary negative symptoms’ and they consider them in relationship with deterioration of social function during puberty, while attention impairment and poverty of content of speech are perceived in relationship with cognitive disturbance and poor school performance of such patients in the premorbid era of their illness. Neither of the aforesaid functions seems to have any association with symptoms of the second group, like Avolition-Apathy or Anhedonia-Asociality [6]. But according to a number of studies [7-14], such kind of categorization of negative symptoms into ‘enduring vs transient’, and ‘primary vs secondary’ may not be essentially maintainable because firstly it may induce bias respecting manageability of negative symptoms and secondly prevent application of necessary interventions and researches based on subjective judgment.

Maybe, that kind of deficit symptoms that are due to disturbances of mood, anxiety, positive symptoms, extra- pyramidal side effects and so on, are only a group of adverse effects that can be managed or ruled out by careful clinical examination, and should not be labeled as ‘negative symptoms’. While the proponents of ‘primary negative symptoms’ discard most of the contrasting clinical studies as non-methodical trials that were dealing mostly with ‘secondary negative symptoms’, it does not look that their evidences regarding negative symptoms are clinically different from other’s proofs. Any idea, like ‘primary’ negative symptoms, that cannot be separated, in any way, from its ‘secondary’ counterpart, is more or less a vague idea. On the other hand, sticking so rigorously to ‘primary’ vs ‘secondary’, based on unclear evidences and subjective inferences, is not truthfully in concord with the fundamental objectives of psychiatric rehabilitation, because promotion of deinstitutionalization is not achievable with endorsement of stigmatization. Hence, in the present assessment, the correctness of aforesaid grouping of negative symptoms and their treatment-refractoriness have been evaluated again in a non-western patient population.

## Methods and Materials



**Figure 1:** Prevalence of negative symptoms among 270 schizophrenic patients

After a primary survey regarding the frequency of negative symptoms among 270 patients with diagnosis of schizophrenia in Razi Psychiatric Hospital, by means of Scale for Assessment of Negative Symptoms (SANS), as main outcome measure, it was evident that 1) virtually no patient was without negative symptoms, and also 2) no particular or comparable arrangement of negative symptoms could be found amongst them, because though a number of patients had analogous harshness in different negative symptoms, but a lot of them had isolated signs with dissimilar severity (Figure 1) [7]. Following the aforesaid study, and in a series of double-blind clinical trials (n=3), the effectiveness of different adjunctive drugs for improvement of apparently ‘primary negative symptoms’ had been assessed, based on a certain inclusion and exclusion criteria (depression, schizoaffective, mental retardation, bipolar disorders, neurological disorders, using atypical antipsychotics, using antidepressants or lithium, medical complications, unstable or irritable or aggressive patients, duration less than one year, parkinsonism, medical deafness or muteness.

Diagnosis of schizophrenia, as well, had been based on the main diagnostic criteria of Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition, Text Revision. In line with the results, in the first tryout (n=40), it had been revealed that citalopram, alprazolam, and clomipramine, in minimum to moderate doses, were meaningfully more effective than placebo (P<0.001, P<0.01 and P<0.01, respectively) in reducing the score of SANS for different sub-scales, individually, around 20% in comparison with baseline (Table 1) [8].

Negative Symptoms Drugs	Affecting Blunting		Alogia		Avolition Apathy		Anhedonia Asociality		Attention Deficit		Total	
	No of patient	Percent	No of patient	Percent	No of patient	Percent	No of patient	Percent	No of patient	Percent	No of patient	Percent
Citalopram 20-40 mg	5	50%	4	40%	4	40%	3	30%	4	40%	8	80%
Alprazolam 0.75-1.5 mg	3	30%	3	30%	4	4%	2	20%	2	20%	5	50%
Clomipramine 25-50 mg	4	40%	2	20%	1	10%	3	30%	3	30%	5	50%
Placebo	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%

Table 1: Response of participants in the first trial by at least 20% decrease in SANS' subscales

In the second study (n=100), effectiveness of bromocriptine, fluoxetine and nortriptyline were compared with placebo. According to the results of this experiment, as well, while all of the used adjunctive drugs, in minimum to moderate doses, were better than placebo, only nortriptyline was significantly more effective (P<0.005) (Table 2) [9]. In third trial (n=30), the effectiveness of maprotiline and fluvoxamine were compared with placebo, and according to the results, both of them were more effective than placebo, though it was significant only with respect to maprotiline (P<0.01) (Table 3) [10, 11]. Totally, in 31.2%, 28%, 26.4%, 24% and 22.4% of the patients there was around 20% reduction in the severity of ‘Attention Deficit’, ‘Alogia’, ‘Affective Blunting’, ‘Anhedonia- Asociality’ and finally ‘Avolition-Apathy’, respectively (Figure 3). Comparable results, as well, have been found in other analogous studies [12-15] (Figure 2).

Negative Symptoms Drugs	Affecting Blunting		Alogia		Avolition Apathy		Anhedonia Asociality		Attention Deficit		Total	
	No of patient	Percent	No of patient	Percent	No of patient	Percent	No of patient	Percent	No of patient	Percent	No of patient	Percent
Bromocriptine 2.5-5 mg	3	24%	5	20%	3	12%	3	12%	6	24%	11	44%
Fluoxetine 20-40 mg	4	16.60%	4	16.60%	7	29.10%	2	8.30%	10	41.60%	15	62.50%
Nortriptyline 25-50 mg	6	24%	9	36%	8	32%	9	36%	10	40%	20	80%
Placebo	2	8.30%	6	25%	1	4.10%	4	16.60%	6	25%	9	37.50%

Table 2: Response of participants in the second trial by at least 20% decrease in SANS' subscales

Negative Symptoms Drugs	Affecting Blunting		Alogia		Avolition Apathy		Anhedonia Asociality		Attention Deficit		Total	
	No of patients	Present %	No of patients	Percent %	No of patients	Percent %	No of patients	Percent %	No of patients	Percent %	No of patients	Percent %
Bromocriptine 2.5-5 mg	3	24%	5	20%	3	12%	3	12%	6	24%	11	44%
Fluoxetine 20-40 mg	4	16.60%	4	16.60%	7	29.10%	2	8.30%	10	41.60%	15	62.50%
Nortriptyline 25-50 mg	6	24%	9	36%	8	32%	9	36%	10	40%	20	80%
Placebo	2	8.30%	6	25%	1	4.10%	4	16.60%	6	25%	9	37.50%

Table 3: Response of participants in the third trial by at least 20% decrease in SANS' subscales

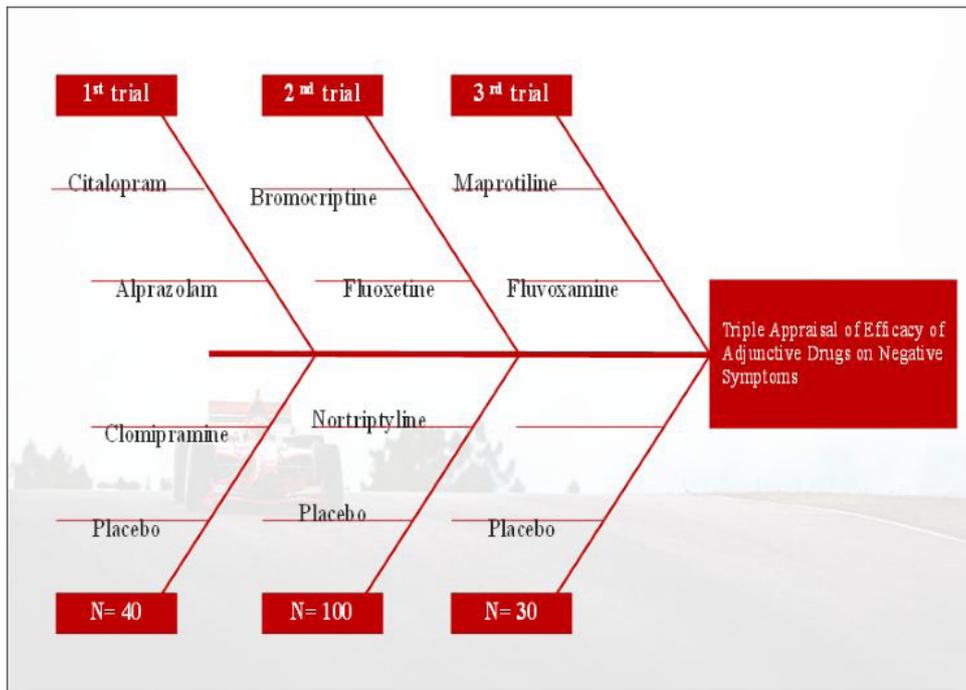


Figure 2: Tripartite study for assessment of effectiveness of adjunctive drugs on negative symptoms



[20% decrease in at least one sub-scale of SANS in comparison with starting point]

Figure 3: General response of patients to add-on medications

## Discussion

As is known, negative symptoms of schizophrenia contribute more to poor functional outcomes and quality of life for individuals with schizophrenia than do positive symptoms [16], and improvement in negative symptoms is associated with a variety of improved functional outcomes including independent living skills, social functioning, and role functioning [17]. Negative symptoms have long been recognized as an integral and clinically important part of schizophrenia. However, the concept has changed over time from Kraepelin’s early description of the destruction of the personality [18], through the domains concept of Strauss and colleagues [19], and Crow’s concept of type II schizophrenia [20], to the operationalization of negative symptoms in SANS, the Positive and Negative Syndromes Scale (PANSS), the Negative Symptom Assessment and others [21,22]. It is mentionable that, though negative symptoms are resistant to treatment and impede functional recovery in schizophrenia, a major challenge to developing efficacious interventions concerns the valid and reliable assessment of negative symptoms [23,24]. An important additional impetus for instrument development was the view that some widely used negative symptom rating scales includes items other than the five recognized domains [25-27].

Likewise, Nancy Andreasen as an important character in schizophrenia study had critiqued the DSM-IV and ICD-10 criteria for losing diagnostic legitimacy for the sake of exaggeratedly enhancement of reliability [28,29]. Today's, some of the practitioners believe that DSM-5 revives the old theory (dating back to at least 1968) that Schizophrenia is a "spectrum" and that we might all fall somewhere on the "continuum" or "spectrum" [30]. For the same reason some of critics point to new categories like "Unspecified Mental Disorder" and "Unspecified Schizophrenia Spectrum Disorder", as factors that make DSM-5 even more vague than its preceding version, DSMIV [31, 32]. Back to our discussion, the following conclusions can be supposed with respect to the abovementioned findings:

1. Absolute pessimistic opinion regarding inflexibility of 'primary negative symptoms' against therapeutic methods does not seem to be tenable and maybe should be revised by clinicians, especially in view of the minimum doses of adjunctive drugs and short duration of assessments in the aforementioned clinical trials.
2. There is no satisfactory proof for grouping 'primary negative symptoms' into two aforesaid groups of 'enduring, treatment-resistant' and 'transient, treatment-responsive' ones.
3. Also, categorization of negative symptoms into 'primary' vs 'secondary' is not without question. Firstly, the DSM-5 itself has not stressed on precise identification of primary ones for diagnosis of schizophrenia. It seems that it has supposed only one type of negative symptoms that are easily diagnosable. Secondly, positive symptoms are in the realm of psychopathology, while negative symptoms are mainly in the realm of social and interpersonal functioning. Function is a multidimensional concept, and its interactional aspect, which is assessed by clinician, may have root in the premorbid traits. Schizotypal, schizoid, avoidant personality disorders, Asperger syndrome or other atypical forms of pervasive developmental disorders, social (pragmatic) communication disorder, and Social anxiety disorder (social phobia) have mannerisms similar to negative symptoms, and while all of them are in the realm of activities, there is no necessity that always and in all situations they ought to be considered dysfunctional.
4. Over again, according to the aforesaid trials, a positive, though limited, response to adjunctive treatments was palpable in the clinical spectrum of negative symptoms. Also, there are so many additional clinical and methodical studies by other researchers, similar to the said studies in the present article, that have shown that negative symptoms are in essence 'treatment-responsive', and there is no necessity to consider it truthful only with respect to 'secondary negative symptoms'. But if, in opposition to the diagnostic criteria of DSM-5, differentiation between 'primary' and 'secondary' in the realm of therapy is so sensitive and hard to accomplish, then maybe it is better to consider them theoretically and totally as 'secondary', instead of 'primary', which can only promote a morbid cycle of stigmatization.
5. Proponents of 'primary negative symptoms', who may have based their suppose on the observable facts of 'disturbance of function', 'chronicity' and 'neuroanatomical changes' of schizophrenic patients, believe principally in the existence of a set of negative symptoms (primary) that are 'treatment-resistant' and 'enduring', not originating from the abovementioned factors. But what kind of 'treatment resistant' is it that easily responds to even the minimum doses of a variety of Specific Serotonin Reuptake Inhibitors (SSRIs), Tricyclic Antidepressants (TCAs) and etc. If the problem is in the apparent reality of 'disturbance of function', then it would be better to be discussed, described or analyzed from that angle. If the neuro-anatomical changes bear in mind the Hughlings Jackson's perspective of 'progressive dissolution of function' and subsequent neurological classification of positive and negative symptoms, nevertheless it should not be ignored that schizophrenia is still in the field of psychiatry.
6. According to Maj M in "Critique of the DSM-IV operational diagnostic criteria for schizophrenia", ".....the five groups of schizophrenia symptoms (delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior and negative symptoms) are all given the same weight in the diagnostic process. The combination of grossly disorganized behavior and alogia qualifies for the diagnosis of schizophrenia as well as the co-occurrence of delusions and hallucinations. This is likely to create difficulties in community mental health setting, where the issue of the differential diagnosis between mental illness and social deviance often arises. Should any vagrant who displays grossly disorganized behavior (for example be appearing markedly disheveled or dressing in an unusual manner) and poverty of speech be diagnosed schizophrenia [33]?"

These were in addition to the quality that the symptomatological criterion could not typify schizophrenia as a disorder, and the vagueness of the threshold beyond which the clinical signs listed in the criterion should be looked upon as symptoms. So far, DSM-5 has solved the first criticism by asserting that: '... At least one of these symptoms must be the clear presence of delusions, hallucinations, or disorganized speech....' But, regarding negative symptoms, and based on the aforementioned trials, they are miscellaneous and show diverse severities, even in an individual patient. A clinician rarely diagnose schizophrenia based on a combination of derailment and apathy, world salad and alogia, persecutory delusion and anhedonia, elementary or functional hallucination and inattention, idea of reference and avolition, and so on, without considering the constellation of symptoms plus duration, insight and function.

If the importance of negative symptoms, in essence, is due to their functional consequences, thus maybe it is better to lay them off as part of the diagnostic principle of schizophrenia (criterion A) and consider them solely in the Criterion B of diagnostic criteria, which considers the level of functioning in one or more major areas, such as work, interpersonal relations, or self-care. While such an approach seems to lessen the risk of clinician's subjective judgment and mislabeling, it increases the objective method of diagnosis of schizophrenia. On the other hand, Wolfgang Gaebel, as chair of the ICD-11's Working Group on the Classification of Psychotic Disorders (WGPD), doubts that whether functional deficiency should be counted as a distinct specifier, and whether it should be an obligatory element of the schizophrenia diagnosis, because he believes that the ICD-11 criteria should be universally applicable [34]. Such a perspective has reverberations comparable to the critical point of view that has been investigated here.

## Conclusion

As said by the outcomes of the current study, classification of negative symptoms into ‘primary vs. secondary’, ‘enduring vs. transitory’ and ‘treatment-resistant vs. treatment-responsive’, may not be essentially defensible. Moreover, negative outlook concerning inflexibility of ‘primary negative symptoms’, against existing therapeutic methods demands renovation.

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