Review Article

RFP Indian Journal of Medical Psychiatry
Volume 4 Number 1, January – June 2021

Pharmacological Management of Negative Symptoms in Schizophrenia

Suprakash Chaudhury[1], Subodh Kumar[2], Biswajit Jagtap[3], Daniel Saldanha[4]

Abstract

Emotional blunting, alogia, avolition, a sociality and anhedonia are features of negative symptoms. Negative symptoms are blamed for poor outcome and persistent disability in schizophrenia. The high hopes of cure of negative symptoms by SGAs have been belied. Due to the complex nature of negative symptoms, several methodological issues are raised and it is treated with different antipsychotics and novel agents with varied results. The development of innovative treatment and increased collaboration is needed to overcome the current limitation.

Keywords: Negative Symptoms; First Generation Antipsychotics; Second Generation Antipsychotics.

How to cite this article:

Suprakash Chaudhury, Subodh Kumar, Biswajit Jagtap, Daniel Saldanha/Pharmacological Management of Negative Symptoms in Schizophrenia/RFP Indian Journal of Medical Psychiatry. 2021;4(1):9–20.

Introduction

In various early studies different definitions for negative symptoms were used. To overcome this problem, an agreed upon definition for negative symptoms includes alogia, avolition, asociality, blunted affect and anhedonia i.e. inability to experience pleasure.[1] The term negative symptom was recommended as a descriptive term with no consideration given to its cause, duration or longitudinal stability. In contrast to this, primary and secondary negative symptoms describe subgroups of negative symptoms with divergent causes, longitudinal course, and identified by longitudinal examination rather than cross-sectional assessment. Primary negative symptoms are thought to be fundamental to schizophrenia, while secondary negative symptoms are believed to be associated with, or produced by, positive symptoms, mood symptoms, side-effects of antipsychotic drugs, social deprivation, or other treatment- and illness- related factors. Negative symptoms are described as "persistent negative symptoms" if they are present for 6 months or more and "deficit syndrome" if they are present for more than 12 months.[2] Clinically significant negative symptoms occur in 50-90% of the patients at onset of schizophrenia.[3] On assessment of schizophrenia patients by a psychiatrist with SANS it was found that two-thirds of the patients suffered from negative symptoms but according to the patients' own estimate the figure was just under 40%.[4] Overall, patients having negative symptoms may have decreased awareness of the adverse effects of these symptoms. In addition they may not notice or care about these symptoms if they are cognitively

Author's Affiliation: [1,4]Professor & Head, Department of Psychiatry, Dr DY Patil Medical College, Dr DY Patil Vidyapeeth, Pimpri, Pune, Maharashtra 411018, India [2]Professor & Head, Department of Psychiatry, Ranchi Institute of Neuropsychiatry & Allied Sciences, Ranchi 834006, Jharkhand, India, [3]Professor & Head, Department of Psychiatry, Rural Medical College, Pravara Institute of Medical Sciences, Loni, Maharashtra 413736, India.

Correspondence Author: Suprakash Chaudhury, Professor & Head, Department of Psychiatry, Dr DY Patil Medical College, Dr DY Patil Vidyapeeth, Pimpri, Pune, Maharashtra 411018, India.

Email: suprakashch@gmail.com

compromised or unemotional. Negative symptoms have adverse effects on patients' functional status, quality of life and long-term outcome.[5] In this paper we discuss the pharmacological management of negative symptoms.

Methodological Issues

Several methodological issues for drugs are raised due to the complex nature of negative symptoms. First, investigators must exclude patients with negative symptoms attributable to neuroleptic akinesia or depression. Negative symptoms as assessed by the BPRS can be reliably differentiated from symptoms of depression.[6] Some investigators have given brief trials of anticholinergic agents or have reduced neuroleptic dosage prior to randomizing patients in drug trials in order to minimize negative symptoms that are secondary to neuroleptic toxicity. However, in a sample of 22 medicated schizophrenia patients with prominent negative symptoms, addition of high-dose benztropine, a substantial reduction of neuroleptic dose (both performed under double-blind conditions) or a trial of desipramine did not significantly alter ratings of negative symptoms. Although the small sample size limited the investigators' power to detect an effect of these interventions, this study does indicate that the confounding effects of parkinsonian side effects and depression on assessment of negative symptoms is probably of relatively small magnitude.[7]

This impression is further supported by the relatively small improvement in negative symptoms associated with neuroleptic dose reduction.[8] Secondly, improvement in positive symptoms at times secondarily decreases ratings of negative symptoms. Therefore, it is problematic to assess specific efficacy for negative symptoms of drugs that are concurrently improving positive symptoms. However, long-term follow-up studies have generally shown that negative symptoms remain relatively stable even when other symptoms improve, thereby suggesting that successful treatment of positive symptoms may not signify a major confounding effect on assessment of negative symptom response.[9]

Finally the interpretation of findings from trials that lack placebo control is potentially more problematic. Although primary negative symptoms generally remain relatively stable over time, placebo-controlled trials demonstrated that patients receiving placebo added to their neuroleptic may display substantial improvement in ratings of negative symptoms.[10]

First Generation Antipsychotics

Evaluation of pooled data from clinical trials of haloperidol or chlorpromazine for treatment of schizophrenia revealed that positive symptoms decreased by 51.5% while negative symptoms diminished by 35%.[11] Whether negative symptoms respond in parallel to positive symptoms or not continues to be debated; two small trials[12] found no relationship between the two but one trial[13] reported significant correlations between response of negative and positive symptoms. One study found that Fluphenazine reduced negative symptoms and the improvement did not correlate with changes in positive symptoms.[14] The improvement in negative symptoms by phenothiazines in five large-scale placebo-controlled studies was likely to be secondary to improvement in positive symptoms.[15] A double-blind randomized trial reported that 20 mg per day of haloperidol produced markedly higher levels of akinesia as compared to 5 or 10 mg per day of the drug.[16]

This level of akinesia falsely shows as negative symptoms on most scales. Similarly, patients receiving conventional doses of fluphenazine decanoate (25 mg every 2 weeks) displayed significantly higher levels of apathy and dysphoria after 1 or 2 years than those receiving low doses (5 mg every 2 weeks). Between plasma fluphenazine concentrations and measures of akinesia, a weak relationship was found.[17] In summary, despite a long-standing view to the contrary, conventional neuroleptics do improve negative symptoms but whether these constitute "primary" negative symptoms cannot be conclusively determined. Although dose-response relationships have not been well established, available evidence suggests a curvilinear relationship with negative symptoms worsening at higher doses of FGAs, probably due to the emergence of antipsychotic-induced akinesia.

Second Generation Antipsychotics

Clozapine. Clozapine produced significantly greater improvement in negative symptoms than did chlorpromazine in a 6-week trial in 268 patients with prominent psychotic symptoms resistant to conventional neuroleptics.[18] Schizophrenia patients (n=39) with residual negative and/or positive symptoms ('partial responders') and a low level of EPS, after an open prospective six-week trial of fluphenazine, randomly received double-blind clozapine or haloperidol for 10 weeks. An overall improvement in psychopathology was seen in both groups. Though the SANS score decreased by 6% in the clozapine group while in the haloperidol

group the SANS score increased by 11%, the difference was not statistically significant. The study indicated that for treating positive symptoms clozapine was superior to haloperidol while effects on negative symptoms was quite minor and they were attributed to differential effects on secondary symptoms.[19] Similar findings were reported by Conley et al.[20] In contrast, another study reported a significant reduction of negative symptoms during a 6-week trial of clozapine in 36 neuroleptic-resistant patients with high levels of negative symptoms at baseline.[21] A 6-week open trial of clozapine in 29 treatment-refractory schizophrenia patients found a 31%, 32% and 35% improvement respectively of negative symptoms, positive symptoms, and disorganization. Improvement of negative symptoms correlated significantly with improvement of disorganization but not with improvement of positive symptoms, depression, or EPS.[22]

In contrast, two open trials of clozapine found that response of negative symptoms correlated with response of positive symptoms and of EPS. Patients with high and low levels of positive symptoms at baseline showed similar reductions, even after adjustment for changes in EPS and depression.[23,24] Kane et al. monitored response of negative symptoms in relation to change in EPS in 56 treatment-resistant schizophrenia patients following a medication-free period that averaged 17 days. Only one of ten items on the Simpson-Angus Scale–akinesia was correlated to the changes in negative symptoms.[25] In a 8-week trial, negative symptoms showed significant response to clozapine but none for olanzapine, risperidone or haloperidol.[26]

Risperidone: A beneficial effect of risperidone on negative symptoms was reported in early comparative trials against haloperidol or perphenazine but there were no significant differences in efficacy between risperidone and the comparators. in an eight-week, multicentre, double-blind study, the improvement in the negative sub-scale of the PANSS was significantly greater in patients receiving risperidone 6 mg/day than those receiving placebo, together with a trend towards superiority over haloperidol. The study comprised of 135 subjects with both positive and negative symptoms in which fixed doses of risperidone (2, 6, 10 or 16 mg/day) were compared with haloperidol (20 mg/day) and placebo. Scores on the EPS Rating Scale increased with the dose of risperidone.[27] These findings were confirmed by an identical multicentric study.[28] In patients with predominant negative symptoms risperidone (mean dose 4.9 mg) was compared to olanzapine (mean dose 12.2 mg). At the end of one year olanzapine showed significant advantages over risperidone in reducing negative symptoms. By path analysis co-varying for EPS, depression and positive symptoms, it was suggested that 52% of the improvement was due to a direct effect and 43% by amelioration of positive symptoms.[29] Studies on general negative symptoms gave contradictory results: as effective as clozapine[30] and olanzapine[31]; not as effective as olanzapine[32]; effective in improving negative symptoms but no differential treatment effects compared to haloperidol[33], perphenazine[34] and zuclopenthixol[35]; not effective in improving negative symptoms and no differential treatment effects compared to haloperidol.[36]

Open studies have reported mixed results: positive effects in improving negative symptoms [37] and negative effects.[38] Risperidone long-acting injectable treatment showed marked improvement in negative symptom severity and it was well tolerated in patients with largely negative symptoms, who switched from a stable antipsychotic regimen.[39]

Olanzapine: Tollefson and Sanger demonstrated that olanzapine had superior effect compared to placebo or haloperidol in subgroups with prominent negative symptoms.[40] In deficit and non-deficit groups categorized using the SDS no improvement occurred in the deficit group suggesting no direct effect.[41] The superiority of olanzapine over risperidone was shown by path analysis and 52% of the effect was due to effects on positive symptoms.[29] Olanzapine's efficacy against general negative symptoms has also been demonstrated in many double-blind trials: superior[42] or similar effect to risperidone[43]; superior effect compared to haloperidol[44] or placebo[45]. Breier and Hamilton also observed greater improvement in depression along with negative symptoms.[44] In treatment resistant schizophrenia neither olanzapine nor chlorpromazine were effective against negative symptoms in subjects with a mean duration of illness of 20 years.[46] The results of a large, six-week placebo-controlled comparison of olanzapine at three dosage levels with haloperidol (10-20 mg/day) in 335 people with schizophrenia in acute exacerbation showed that at the highest dose used (12.5-17.5 mg/day) olanzapine produced a significantly greater improvement in the SANS rating than either haloperidol or placebo. As compared to placebo low dose (2.5- 7.5 mg) had a greater effect on SANS ratings. A path analysis of

this trial estimates that 55% of the superior efficacy of high-dose (mean 15 mg/day) olanzapine to placebo on negative symptoms can be attributed to a direct effect.[47]

Quetiapine: In a placebo-controlled multi-centered study comprising of 286 patients which studied both a low (up to 250 mg/day) and a high (up to 750 mg/ day) dose range compared to placebo a significant superiority was reported for higher dose range in patients assessed by the SANS, but not in those assessed by the PANSS. In 201 patients assessed with negative symptom sub-scale of PANSS treated for six weeks with similar doses of quetiapine and chlorpromazine (up to 750 mg daily), despite greater improvement in the quetiapine group, the difference was not statistically significant.[48] A double-blind, placebo controlled multidose comparison of 6 wks in 361 patients using Quetiapine (75, 150, 300, 600, or 750 mg/d), haloperidol (12 mg/d), or placebo, revealed that Quetiapine 300 mg/d was significantly superior only for negative symptoms.[49] Similar findings were reported by two studies[50,51], but another study found no significant difference between treatment groups in double-blind comparison of Quetiapine and chlorpromazine.[52]

Amisulpride: Amisulpride preferentially blocks pre-synaptic dopamine auto-receptors at low doses, whereas at higher doses it also blocks post-synaptic dopamine receptors. Its atypical profile may account for the clinical efficacy on positive symptoms of schizophrenia at high doses and on negative symptoms at low doses and its low propensity to induce extra pyramidal side-effects. A multi-centre, double-blind placebo controlled six week trial of amisulpiride showed that the mean SANS score decreased by 22.8% in the placebo group, 40.6% with 100 mg/day amisulpiride and 45.9% with 300 mg/day amisulpiride.[53]

Another placebo controlled amisulpride (100 mg/day) trial in 141 schizophrenia patients with predominantly negative symptoms over six months found significantly more responders in the amisulpiride group compared to the placebo group.[54] A meta-analysis found a small but significant effect size compared with placebo (r=0.26; pb0.0001) and a smaller, insignificant effect size compared with typical antipsychotics (r=0.08).[55] The effect of amisulpride on primary negative symptoms is consistent although modest when compared to placebo. In an open label study 40 consecutive adult inpatients with schizophrenia were treated with one of the two drug regimens, i.e. tab Amisulpride (100-300 mg/day) and tab Olanzapine (10-20 mg) for 60 days. Despite significant improvement in negative and cognitive symptoms from baseline to endpoint in both the groups, there was no significant difference between amisulpride and olanzapine group.[56]

Sertindole: In an early placebo-controlled clinical trial 28 days' treatment with sertindole (8, 12 and 20 mg daily) showed comparable efficacy with haloperidol (16 mg daily) in all measures (PANSS, BPRS and CGI) including those of negative symptoms.[57] A multi-centric dose-ranging study of four doses of sertindole (8, 16, 20 and 24 mg) and one dose of haloperidol (10 mg) in 617 schizophrenia patients reported that sertindole (16 mg) was significantly more effective than haloperidol in reducing negative symptoms.[58] Similar findings were also reported in a European dose-finding study.[59] Positive, depressive and extrapyramidal symptoms were controlled in both analysis.

Zotepine: In a double-blind, randomised comparison in 30 people with schizophrenia of the residual type with prevailing negative symptoms, zotepine had superior efficacy to haloperidol. Zotepine significantly decreased the ratings for flattening of affect, alogia, social withdrawal and attention deficit but haloperidol failed to improve any of the individual SANS factors. Patients on haloperidol also had significantly higher EPS.[60] In another study outpatients who had prominent negative symptoms with no acute exacerbation for at least 5 months a positive effect was reported.[61] After controlling for positive symptoms, depression and EPS zotepine treatment resulted in striking reduction in negative symptoms, but it was not significantly different in comparison to placebo.[62]

Aripiprazole: A one-year double-blind trial comparing aripiprazole (30 mg) to haloperidol (10 mg) a significant reduction in the PANSS negative subscale was observed in the aripiprazole group.[63] In comparison with placebo, Aripiprazole has demonstrated greater improvement in general negative symptoms.[64] Aripiprazole augmentation of clozapine resulted in decrease of refractory negative symptoms in a series of three case studies.[65]

Ziprasidone: In a six-week trial of 302 people with acute exacerbations of schizophrenia or schizoaffective disorder, Ziprasidone (80 or 160 mg/day) was significantly superior to placebo with respect to both positive and negative symptoms (BPRS, PANSS, CGI)[66] In a placebo control trial, Ziprasidone (80–160 mg/day) was significantly superior in treating general negative symptoms with similar efficacy to olanzapine 10 mg/day[45] and risperidone 6 mg/day.[28] This finding was

replicated in a 12-month study.[67] Ziprasidone treatment of resistant schizophrenia over 12 weeks resulted in a significant decrease in the PANSS negative subscore compared to chlorpromazine.[68] Ziprasidone (mean dose 118 mg) and amisulpride (mean dose 145 mg) had similar efficacy in the treatment of undifferentiated, prominent negative symptoms as measured by the PANSS negative subscale.[69]

Paliperidone: Paliperidone, the major active metabolite of risperidone, is an antagonist at D2,5HT2A, α1 and α 2 adrenergic and H1-histaminergic receptors. It has been found to be safe and effective in the treatment of negative symptoms in both acute and chronic schizophrenia.[70-73]

Iloperidone: Iloperidone is an antagonist at 5HT2C, 5HT6, D3 and D4 receptors and a partial agonist at 5HT1A receptors. It reduced schizophrenic symptoms at oral doses from 12 to 24 mg in double blind phase III trials. Compared to placebo, iloperidone decreased PANSS total score and BPRS scores more effectively; in post-hoc analysis it was as effective as haloperidol and risperidone.[74]

Blonanserin: Blonanserin is a new atypical antipsychotic agent with high binding affinity for D2,3 and 5-HT2A receptor subtypes. Unlike some other atypical antipsychotics, blonanserin has low affinity for other neurotransmitter receptors, including M1, H1, and α1-adrenergic receptors which may minimize its potential to induce certain adverse effects, such as dry mouth, weight gain/ sedation and orthostatic hypotension respectively.

In comparison with other antipsychotic agents, results from a randomized, double-blind, multicentre, short-term trial in patients with schizophrenia indicate that blonanserin is non-inferior to haloperidol with regard to rates of final global improvement. However, blonanserin showed more effectiveness in improving the PANSS negative symptoms sub-score than haloperidol.[75]

Asenapine: Asenapine has a unique receptor binding profile; it displays high affinity binding and antagonistic activity at a wide range of dopamine (D3 andD2S and D2L), serotonin (5-HT2C, 5-HT2A, 5-HT7, 5-HT2B and 5-HT6), noradrenaline (α2B-adrenergic) and histamine (H1 and H2) receptors, but has partial agonist activity at 5-HT1A receptors. Asenapine treatment of acute schizophrenia patients produced a significant decrease in PANSS total score compared to placebo at 6 weeks. At 26 weeks, asenapine and olanzapine reduced the total score of Negative Symptom Assessment (NSA-16) from baseline to a similar extent in schizophrenia patients with predominant, persistent, negative symptoms.[76]

Lurasidone: Lurasidone is an antagonist of dopamine D2 and D3 and serotonin 5-HT7 receptors and a partial agonist of 5HT1A receptors. A post hoc analysis of 5 trials of Schizophrenia patients (n=256) with prominent negative symptoms treated with 40-160 mg Lurasidone after 6 weeks showed significantly greater improvements in PANSS total score and PANSS negative subscale score, compared to placebo.[77]

Cariprazine: Cariprazine a new antipsychotic is a partial agonist of dopamine D3-preferring D3/ D2 receptor and serotonin 5-HT1A receptor. A prospective trial of schizophrenia patients with predominant and persistent negative symptoms revealed that cariprazine was significantly more effective than risperidone in treating negative symptoms.[78]

Comparison of FGA and SGA

The Clinical Antipsychotic Trials of ntervention Effectiveness (CATIE)[79] and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS)[80] were large clinical trials which compared the FGAs with the SGAs. These trials did not show any significant differences in reduction symptoms of psychosis, rates of treatment discontinuation, or improvement in quality of life between FGAs and SGAs. Both trials found no difference in treatment response between FGAs and SGAs, though SGAs had a lower risk of tardive dyskinesia. CATIE also did not find SGAs to be superior to FGAs in decreasing negative or cognitive symptoms of schizophrenia. A multi-treatment meta-analysis of randomized controlled trials (RCTs) in 2012 revealed that in schizophrenia patients all antipsychotic medications were significantly more effective than placebo.[81] A more recent meta-analysis showed similar efficacy of FGA and SGA. In this meta-analysis the most efficacious antipsychotics were amisulpride, olanzapine, risperidone and clozapine.[82]

Glutamatergic Agents: Glycine and D-cycloserine potentiate neurotransmission by binding to the NMDA receptor complex, which plays a key role in the glutamate model of schizophrenia. Twenty two treatment-resistant schizophrenia patients with persistent negative symptoms were treated with 0.8 g/kg per day of glycine added to their ongoing antipsychotic medication in a double-blind, placebo-controlled, 6-week, crossover trial.[83] Glycine administration resulted in a significant 30% + 16% reduction ($P < 0.001$) in PANSS negative symptoms. Limitation of the study was that glycine

also improved positive symptoms significantly, which may have contributed to the observed negative symptom effect and underscores the importance of limiting the severity of positive symptoms. Significant reduction [decrease] in negative symptoms independent of positive symptoms, EPS or depression has been reported by some studies. All sample sizes were small (range 9–22) and only one study investigated effects on primary negative symptoms; the other studies co-varied for secondary factors in their analyses.[84] Studies with clozapine have reported significant worsening of negative symptoms on addition of Dcycloserine[85] but no changes on addition of glycine.[86]

SSRI as add on: Silver and Nassar studied 30 chronic schizophrenia inpatients with SANS global item score of 3 or more and limited positive symptoms, on stable doses of typical antipsychotics. Fluvoxamine (50 mg/day in the first week then 100 mg/day) or placebo were added to the treatment for 5 weeks. A significant reduction in total SANS score was observed in the fluvoxamine group compared to placebo.[87] Silver and Shmugliakov compared fluvoxamine with maprotiline as add on in 25 inpatients of chronic schizophrenia with prominent negative symptoms. The fluvoxamine-treated group showed significant improvement in SANS total score, affective flattening and alogia compared to the maprotiline group and no change was found in MADRS scores, positive symptoms or EPS in either treatment group.[88] Study comparing add-on fluvoxamine (50–100 mg/day) or placebo in 53 chronic schizophrenia patients with high baseline SANS (mean 72) and SAPS (mean 45) scores reported that fluvoxamine treatment showed significant improvement in negative symptoms when compared to placebos.[10] Positive, depressive and EPS symptoms did not change with either treatment. Similar results were obtained with fluoxetine (20mg/day).[89,90]

The improvement in negative symptoms increased steadily over the treatment period, suggesting that more clinical improvement may have been achieved with longer treatment. Arango et al. reported no improvement in negative symptoms with add-on fluoxetine.[91] Buchanan et al. found no benefit in augmenting clozapine with fluoxetine.[92] Salokangas et al. compared citalopram (40 mg/day) and placebo added to typical neuroleptics in 90 chronic schizophrenic outpatients with PANSS scores higher than 50. A significant decrease in total PANSS was found in both groups after 12 weeks but there were no significant differences between them.[93]

Lee et al. found no significant change in positive, negative or general psychopathology factors of the PANSS or the CGI Scale after 8 weeks of addition of sertraline (50mg/day; n=18) or placebo to haloperidol treatment of inpatients with chronic schizophrenia.[94] A similarly designed PCT found a significant improvement in PANSS negative subscale scores when patients on a antipsychotics were augmented with paroxetine 30 mg[95] and also with Mirtazepine.[96] Mirtazepine was similarly beneficial when used to augment clozapine therapy in an 8-week placebo controlled trial (PCT) of 30 patients.[97] But Reboxetine, failed to improve negative symptoms in a PCT.[98] A Recent Cochrane systematic review concluded based on very low quality evidence that compared to placebo, NRIs (specifically reboxetine) may be beneficial in the treatment of negative symptoms of schizophrenia.[99] Currently, evidence from open studies suggest that in some patients SSRI augmentation of atypical antipsychotics may benefit patients but further research is warranted.

Selective Monoamine Oxidase B Inhibitors: Bodkin and colleagues studied add-on therapy with 5mg/day selegiline on a stable antipsychotic dose in a 12-week PCT in 67 patients with schizophrenia and persistent negative symptoms. SANS total and avolition, apathy and anhedonia global scores, BPRS total score, and CGI severity and improvement scores shows significant changes favoring selegiline over placebo, indicating that selegiline may have a beneficial effect for persistent negative symptoms.[100] A 12-week, double-blind, PCT involving schizophrenia or schizoaffective disorder patients with persistent negative symptoms randomized to receive rasagiline, 1mg/d (n = 31) or placebo (n = 29) revealed significant reduction in SANS total score and avolition subscale scores with rasagiline at the end of 12 weeks.[101]

Novel Agents: Novel agents like dehydroepiandrosterone[102,103] deprenyl[104], Ginkgo,[105] methylene blue[106], naltrexone[107], pergolide[108] and memantine[109] have given some positive results but need further evaluation. Studies with augmentation of essential fatty acids have shown mixed results.[110] while those using estrogens[111] and galantamine[112] were disappointing. Meta-analysis of studies on effects of reputative transcranial magnetic stimulation on negative symptoms of schizophrenia has reported small

improvement in negative symptoms.[113]

Future Challenges

Due to the current limitations in treatment responsiveness, pharmaceutical industry will in the future target negative symptoms and develop innovative either broad-spectrum or adjunctive treatments that would provide valuable additions to our treatment options. Interpretation of clinical trial results is complicated, but hurdles can be managed by the use of appropriate selection criteria, sensitive. For clinicians, meaningful interpretation of any forthcoming data on new adjunctive treatment will depend on a clarification of the neuropathology of negative symptoms, epidemiology, better definition and nosology of negative symptoms. A definitive conceptualization is needed to understand whether negative symptoms should be considered heterogeneous or homogeneous, dimensional or categorical and how they are distributed beyond patients with schizophrenia.

References

1. Kirkpatrick B, Fenton WS, Carpenter WT, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. Schizophrenia Bulletin 2006;32:214-219.
2. Buchanan RW: Persistent negative symptoms in schizophrenia: an overview. Schizophr Bull 2007; 33:1013-22.
3. Malla AK, Norman RGM, Takhar J, Manchanda R, Townsend L, Scholten D, et al. Can patients at risk for persistent negative symptoms be identified during their first episode of psychosis. Journal of nervous and mental disease 2004;192:455-463.
4. Selten J-P, Wiersma D, van den Bosch R. Distress attributed to negative symptoms in schizophrenia. Schizophrenia Bulletin 2000;26: 737-744.
5. Möller HJ. The relevance of negative symptoms in schizophrenia and how to treat them with psychopharmaceuticals .Psychiatria Danubina, 2016; 28 (4): 435-440.
6. Newcomer JW, Faustman WO, Yeh W, Csernansky JG. Distinguishing depression and negative symptoms in unmedicated patients with schizophrenia. Psychiatry Res. 1990;31: 243-250
7. Hogarty GE, McEvoy JP, Ulrich RF, DiBarry AL, Bartone P, Sooley S, et al. Pharmacotherapy of impaired affect in recovering schizophrenic patients. Archives of General Psychiatry.1995;52:2941.
8. Seidman W,Pepple JR, Faraone SV, Kremen WS, Green AI, Brown WA, et al. Neuropsychological performance in chronicschizophrenia in response to neuroleptic dose reduction. BiologicalPsychiatry 1993;33:575-84.
9. Arndt S, Andreasen NC, Flaum M, Miller D, Nopoulos P. A longitudinal study of symptom dimensions in schizophrenia: prediction and patterns of change. Archives of General Psychiatry. 1995;52:35240.
10. Silver H, Barash I, Aharon N, Kaplan A, Poyurovsky M. Fluvoxamine augmentation of antipsychotics improves negative symptoms in psychotic chronic schizophrenic patients: a placebo-controlled study. International clinical psychopharmacology 2000; 15:257–261.
11. Kay SR, Singh MM. The positive-negative distinction in drug-free schizophrenic patients: stability, response to neu-roleptics, and prognostic significance. Archives of General Psychiatry.1989;46:711-8.
12. Serban G, Siege1 S, Gaffney M. Response of negative symptoms of schizophrenia to neuroleptic treatment. The Journal of clinical psychiatry 1992;53:229-34.
13. Tandon R, Goldman R, DeQuardo JR, Goldman M, Perez M, Jibson M. Positive and negative symptoms covary during clozapine treatment in schizophrenia. Journal of psychiatric research 1993;27 341-347.
14. Breier, A., Wolkowitz, O.M., Doran, A.R., Roy, A., Boronow, J., Hommer, D.W., Pickar, D. Neuroleptic responsivity of negative and positive symptoms in schizophrenia. American Journal of psychiatry. 1987; 144, 1549–1555.
15. Goldberg SC. Negative and deficit symptoms in schizophrenia do respond to neuroleptics. Schizophrenia Bulletin. 1985;11:453-6.
16. Van Putten T, Marder SR, Mintz J. A controlled dose comparison of haloperidol in newly admitted schizophrenic patients. Archives of General Psychiatry.1990;47:754-8.
17. Marder SR, Van Putten T, Mintz J, Lebell M, McKenzie J, May PRA. Low- and conventional-dose maintenance therapy with fluphenazine decanoate: two-year outcome. Archives of General Psychiatry.1987;44:518-21.
18. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Archives of General Psychiatry.1988;45: 789- 96.
19. Breier A, Buchanan RW, Kirkpatrick B, Davis OR, Irish D, Summerfelt A, et al. Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. American journal of psychiatry. 1994;151:20-6.

20. Conley R, Richardson C, Kent D, Gounaris C, Zaremba S. Clozapine response varies in deficit vs non-deficit schizophrenic subject. Biological Psychiatry 1994;35:746.

21. Meltzer HY. Clozapine: is another view valid? American Journal of Psychiatry. 1995; 152: 821-5.

22. Miller DD, Perry PJ, Cadoret LJ, Andreasen NC. Clozapine's effect on negative symptoms in treatment-refractory schizophrenics. Comprehensive psychiatry 1994;35:8-15.

23. Tandon, R., Ribeiro, S.C.M., DeQuardo, J.R., Goldman, R.S., Goodson, J., Greden, J.F. Covariance of positive and negative symptoms during neuroleptic treatment in schizophrenia: a replication. Biol. Psychiatry 1993; 34, 495–497.

24. Lieberman JA, SaffermanAZ, Pollack S, Szymanski S, Johns C, Howard A, et al. Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. American journal of psychiatry. 1994;151:1744-52.

25. Kane JM, SaffermanAZ, Pollack S, Johns C, Szymanski S, Kronig M, et al. Clozapine, negative symptoms, and extrapyramidal side effects. The Journal of clinical psychiatry 1994;55(suppl B):74-7.

26. Volavka, J., Czobor, P., Sheitman, B., Lindenmayer, J.P., Citrome, L. et al. Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. American journal of psychiatry. 2002; 159, 255–262.

27. Chouinarad, G Jones, B.,Remington, G.,etal. A Canadian multicentre, placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. Journalof ClinicalPsychopharmacology,1993; 13:25-40.

28. Marder, S.R., Meibach, R.C. Risperidone in the treatment of schizophrenia. American journal of Psychiatry. 1994; 151: 825–835.

29. Alvarez, E., Ciudad, A., Olivares, J.M., et al. A randomized, 1-year follow-up study of olanzapine and risperidone in the treatment of negative symptoms in outpatients with schizophrenia. Journal of Clinical Psychopharmacology. 2006; 26: 238–249.

30. Klieser, E., Lehmann, E., Kinzler, E., Wurthmann, C., Heinrich, K. Randomized, double-blind, controlled trials of risperidone versus clozapine in patients with chronic schizophrenia. Journal of clinical psychopharmacology 1995; 15 (suppl. 1): 45S–51S.

31. Ho BC, Miller D, Nopoulos P, Andreasen NC. A comparative effectiveness study of risperidone and olanzapine in the treatment of schizophrenia. J Clin Psychiatry. 1999;60(10):658-663.

32. Feldman, P.D., Kaiser, C.J., Kennedy, J.S., Sutton, V.K., Tran, P.V., Tollefson, G.D., Zhang, F., Breier, A. Comparison of risperidone and olanzapine in the control of negative symptoms of chronic schizophrenia and related psychotic disorders in patients aged 50 to 65 years. The Journal of clinical psychiatry 2003; 64: 998–1004.

33. Češková, E., Švestka, J. Double-blind comparison of risperidone and haloperidol in schizophrenic and schizoaffective psychoses. Pharmacopsychiatry 1993; 26: 121–124.

34. Høyberg, O.J., Fensbo, C., Remvig, J., Lingjaerde, O., Sloth-Nielsen, M., Salvesen, I. Risperidone versus perphenazine in the treatment of chronic schizophrenic patients with acute exacerbations. Acta psychiatrica Scandinavica. 1993; 88: 395–402.

35. Huttunen, M.O., Piepponen, T., Rantanen, H., Larmo, I., Nyholm, R., Raitasuo, V. Risperidone versus zuclopenthixol in the treatment of acute schizophrenic episodes: a double-blind parallelgroup trial. Acta psychiatrica Scandinavica. 1995;91: 271–277.

36. Borison, R.L., Pathiraja, A.P., Diamond, B.I., Meibach, RC. Risperidone: clinical safety and efficacy in schizophrenia. Psychopharmacology Bulletin. 1992, 28, 213–218.

37. Bersani, G., Bressa, G.M., Meco, G., Marini, S., Pozzi, F., Combined serotonin-5-HT2 and dopamine-D2 antagonism in schizophrenia: clinical, extrapyramidal and neuroendocrine response in a preliminary study with risperidone. Human psychopharmacology. 1990, 5, 225–231.

38. Smith, R.C., Chua, J.W., Lipetsker, B., Bhattacharyya, A. Efficacy of risperidone in reducing positive and negative symptoms in medication-refractory schizophrenia: an open prospective study. The Journal of clinical psychiatry 1996;57: 460–466.

39. Curtis VA, Katsafouros K, Möller HJ. Long-acting risperidone improves negative symptoms in stable psychotic patients. Journal of Psychopharmacology 2008; 22: 254–261.

40. Tollefson, G.D., Sanger, T.M. Negative symptoms: a path analytical approach to a double-blind, placebo- and haloperidolcontrolled clinical trial with olanzapine. Am. J. Psychiatry 1997; 154, 466–474.

41. Kopelowicz, A., Zarate, R., Tripodis, K., Gonzalez, V., Mintz, J. Differential efficacy of olanzapine for deficit and nondeficit negative symptoms in schizophrenia. Am. J. Psychiatry 2000; 157: 987–993.

42. Tran, P.V., Hamilton, S.H., Kuntz, A.J., Potvin, J.H., Andersen, S.W., Beasley Jr., C., Tollefson, GD. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. Journal of Clinical Psychopharmacology. 1997;17: 407–418.
43. Conley, R.R., Mahmoud, R. A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. Am. J. Psychiatry 2001;158: 765–774.
44. Breier, A., Hamilton, S.H. Comparative efficacy of olanzapine and haloperidol for patients with treatment-resistant schizophrenia. Biol. Psychiatry 1999;45: 403–411.
45. Beasley, C.M., Tollefson, G., Tran, P., Satterlee, W., Sanger, T., Hamilton, S. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 1996a, 14, 111–123.
46. Heres, S., Davis, J., Maino, K., Jetzinger, E., Kissling, W., Leucht, S. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. Am. J. Psychiatry 2006;163: 185–194.
47. Beasley,C.M., Sanger, T., Satterlee,W., Tollefson, G., Tran, P.,Hamilton, S. Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. Psychopharmacol 1996b, 124, 159–167.
48. Arvanitis, L. Clinical profile of Seroquel (ICI 204, 636): an overview of recent clinical studies. In: Holliday, S., Ancill, R.J., MacEwan, G.W. (Eds.), Schizophrenia: Breaking down the Barriers. John Wiley, New York,1996.
49. Arvanitis LA, and Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Biological Psychiatry 1997;42:233-46.
50. Borison, R.L., Arvanitis, L.A., Miller, B.G. ICI 204, 636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo- controlled trial in patients with schizophrenia Journal of clinical psychopharmacology 1996;16: 158–169.
51. Hurst, B.C., Link, C.G.G. 'Seroquel' (ICI 204, 636) Efficacy in treating the negative symptoms of schizophrenia. European Neuropsychopharamacology. 1996 ; 6(Suppl. 4): S4–124.
52. Peuskens J, Link C. A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. Acta psychiatrica Scandinavica. 1997;96:265-73.
53. Boyer, P., Lecrubier, Y., Puech, A.J., Dewailly, J., Aubin, F. Treatment of negative symptoms in schizophrenia with amisulpride. Br. J. Psychiatry 1995;166: 68–72.
54. Loo, H., Poirier-Littre, M.F., Theron, M., Rein, W., Fleurot, O., Amisulpride versus placebo in the medium-term treatment of the negative symptoms of schizophrenia. Br. J. Psychiatry 1997 ; 170: 18–22.
55. Leucht, S., Pitschel-Walz, G., Engel, R.R., Kissling, W. Amisulpride, an unusual "atypical" antipsychotic: a meta-analysis of randomized controlled trials. Am. J. Psychiatry 2002, 159, 180–190.
56. Kumar S, Chaudhury S. Efficacy of amisulpride and olanzapine for negative symptoms and cognitive impairments: An open-label clinical study. Industrial Psychiatry Journal 2014;23:27-35.
57. Targum, S., Zborowski, J., Henry, M., Schmitz, P., Sebree, T.,Wallin, B. Efficacy and safety of sertindole in two double-blind, placebo controlled trials of schizophrenic patients. European Neuropsychopharamacology. 1995; 5 (3): 348.
58. Hale, A., Van der Burght, M., Friberg, H.H., Wehnert, A. Dose ranging study comparing 4 doses of sertindole and 1 dose of haloperidol in schizophrenic patients. European Neuropsychopharmacology. 1996; 6 (Suppl. 3): 61.
59. Wehnert, A., Mack, R., Stilwell, C., Rasmussen, C., Silber, C.H. Direct effect of sertindole on the primary negative symptoms of schizophrenia: a path analysis. Biol Psychiatry 1997; 42: 188S.
60. Barnas, C., Stuppäck, C.H., Miller, C., Haring, C., Sperner- Unterweger, B., Fleischhacker, W.W. Zotepine in the treatment of schizophrenic patients with prevailingly negative symptoms: a double-blind trial vs. haloperidol. International clinical psychopharmacology Int. Clin. Psychopharmacol. 1992; 7, 23–27.
61. Fleischhacker, W.W., Barnas, C., Stuppäck, C., Unterweger, B., Hinterhuber, H. Zotepine in the treatment of negative symptoms in chronic schizophrenia. Pharmacopsychiatry1987; 20: 58–60.
62. Möller, H.J., Riedel, M., Muller, N., Fischer, W., Kohnen, R. Zotepine versus placebo in the treatment of schizophrenic patients with stable primary negative symptoms: a randomized double-blind multicenter trial. Pharmacopsychiatry 2004, 37 (6), 270–278.
63. Manos, G., McQuade, R., Stock, E., Archibald, D.G., Tourkodimitris, S., Marcus, R.N., 2003. Long-term effects of aripiprazole on the negative symptoms of schizophrenia. Presented at the American Psychiatric Association

Meeting 2003.

64. Kane, J.M., Carson, W.H., Saha, A.R., McQuade, R.D., Ingenito, G.G., Zimbroff, D.L., Ali, M.W. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. Journal of Clinical Psychiatry. 2002; 63: 763–771.
65. Clarke, L.A., Lindenmayer, J.P., Kaushik, S. Clozapine augmentation with aripiprazole for negative symptoms. Journal of Clinical Psychiatry 2006; 67: 675–676.
66. Reeves, K. The efficacy and safety of two fixed doses of ziprasidone in schizphrenia. European Neuropsychopiwnnacology, 1996;6(suppl.3):201.
67. Arato, M., O'Connor, R., Meltzer, H.Y., ZEUS Study Group. A 1-year placebo-controlled double-blind trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. International Clinical psychopharmacology 2002;17 (5): 207–215.
68. Kane, JM., Khanna, S., Rajadhyaksha, S., Giller, E. Efficacy and tolerability of ziprasidone in patients with treatment-resistant schizophrenia. International clinical psychopharmacology. 2006;21 (1): 21–28.
69. Olie, J.P., Spina, E., Murray, S., Yang, R. Ziprasidone and amisulpride effectively treat negative symptoms of schizophrenia: results of a 12-week, double-blind study. International clinical psychopharmacology. 2006;21: 143–151.
70. Savitz AJ, Xu H, Gopal S, et al. Efficacy and safety of paliperidone palmitate three-monthly formulation in East Asian patients with schizophrenia: subgroup analysis of a global, randomized, doubleblind, Phase III, noninferiority study. Neuropsychiatr Dis Treat 2017;13:2193–207.
71. Schreiner A, Bergmans P, Cherubin P, et al. The effect of longacting paliperidone palmitate once-monthly on negative and depressive symptoms in patients with schizophrenia switched from previous unsuccessful treatment with oral aripiprazole. Ther Adv Psychopharmacol 2017;7:59–65.
72. Gu Y, Peng H, Dai J, et al. Evaluation of paliperidone on social function in patients with chronic schizophrenia. General Psychiatry 2018;31:e000011.
73. Mauri M, Mauri MC, Adami M, et al. Efficacy and tolerability of paliperidone ER in patients with unsatisfactorily controlled schizophrenia by other antipsychotics: a flexible-dose approach. Int Clin Psychopharmacol 2015;30:329–37.
74. Caccia, S., Pasina, L., Nobili, A. New atypical antipsychotics for schizophrenia: iloperidone. Drug Des DevelTher. 2010; 4: 33-48.
75. Deeks, E.D. and Keating, G.M. Blonanserin A Review of its Use in the Management of Schizophrenia. CNS Drugs 2010; 24 (1): 65-84.
76. Weber, J. and McCormack, P.L. Asenapine. CNS Drugs 2009; 23 (9): 781-792.
77. Schooler NR, Pikalov A, Hsu J, Cucchiaro J, Goldman R, Loebel A. Efficacy of lurasidone in the treatment of schizophrenia with prominent negative symptoms: a post-hoc analysis of five short-term trials. Eur Neuropsychopharmacol. 2014; 24 (Suppl 2):S558.
78. Fleischhacker W, Galderisib S, Laszlovszkyc I, Szatmáric B, Barabássyc A, Acsaic K, Szalaic E, Harsányic J, Earleyd W, Patel M, Némethc G. The efficacy of cariprazine in negative symptoms of schizophrenia: Post hoc analyses of PANSS individual items and PANSS-derived factors. European psychiatry 2019; 58: 1-9.
79. Lieberman JA, Stroup TS, McEvoyJP et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia N Engl J Med 2005 ; 353: 1209 –23.
80. Jones PB, Barnes TR, Davies L et al. Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1) Arch Gen Psychiatry 2006; 63: 1079 – 87.
81. Leucht S Tardy M Komossa K et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Lancet 2012; 379: 2063–71.
82. Leucht S Cipriani A Spineli L et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis Lancet 2013; 382: 951–62.
83. Heresco-Levy, U., Javitt, D.C., Ermilov, M., Mordel, C., Silipo, G., Lichtenstein, M. Efficacy of high-dose glycine in the treatment of enduring negative symptoms of schizophrenia. Archives of General Psychiatry. 1999;56: 29–36.
84. Heresco-Levy, U., Ermilov, M., Lichtenberg, P., Bar, G., Javitt, D.C. High-dose glycine added to olanzapine and risperidone for the treatment of schizophrenia Biological Psychiatry 2004; 2: 165–171.
85. Goff, D.C., Henderson, D.C., Evins, A.E., Amico, E.A placebo controlled crossover trial of D-cycloserine added to clozapine in patients with schizophrenia. Biol Psychiatry. 1999;45:512–514.
86. Evins, A.E., Fitzgerald, S.M.,Wine, L., Rosselli,

R., Goff, D.C. Placebo-controlled trial of glycine added to clozapine in schizophrenia. Am J Psychiatry. 2000; 157 (5), 826–828.

87. Silver H, Nassar A. Fluvoxamine improves negative symptoms in treated chronic schizophrenia: an add-on doubleblind, placebo-controlled study. Biological Psychiatry 1992;31:698-704.

88. Silver, H., Shmugliakov, N., 1998. Augmentation with fluvoxamine but not maprotiline improves negative symptoms in treated schizophrenia; evidence for a specific serotonergic effect from a double-blind study. Journal of Clinical Psychiatry 18, 208–211.

89. Goff, D.C., Midha, K.K., Sarid-Segal, O., Hubbard, J.W., Amico, E. A placebo-controlled trial of fluoxetine added to neuroleptic in patients with schizophrenia. Psychopharmacology 1995a ;117: 417–423.

90. Spina, E., De Domenico, P., Ruello, C., Longobardo, N., Gitto, C., Ancione, M., Di Rosa, A.E., Caputi, A.P. Adjunctive fluoxetine in the treatment of negative symptoms in chronic schizophrenic patients. International clinical psychopharmacology. 1994;9: 281–285.

91. Arango C, Kirkpatrick B, Buchanan, RW. Fluoxetine as an adjunct to conventional antipsychotic treatment of schizophrenia patients with residual symptoms. The Journal of nervous and mental disease 2000;188:50–53.

92. Buchanan, R.W., Kirkpatrick, B., Bryant, N., Ball, P., Breier, A. Fluoxetine augmentation of clozapine treatment in patients with schizophrenia. Am J Psychiatry. 1996; 153: 1625–1627.

93. Salokangas, R.K., Saarijarvi, S., Taiminen, T., Kallioniemi, H., Lehto, H., Niemi, H., Tuominen, J., Ahola, V., Syvalahti, E. Citalopram as an adjuvant in chronic schizophrenia: a double-blind placebo-controlled study. Acta Psychiatrica Scand. 1996; 94: 175–180.

94. Lee, M.S., Kim, Y.K., Lee, S.K., Suh, K.Y. A double-blind study of adjunctive sertraline in haloperidol-stabilized patients with chronic schizophrenia. Journal of clinical psychopharmacology. 1998;18: 399–403

95. Jockers-Scherubl, M.C., Bauer, A., Godemann, F., Reischies, F.M., Selig, F., Schlattmann, P. Negative symptoms of schizophrenia are improved by the addition of paroxetine to neuroleptics: a double-blind placebo-controlled study. International clinical psychopharmacology. 2005;20: 27–31.

96. Berk, M., Ichim, C., Brook, S. Efficacy of mirtazepine add-on therapy to haloperidol in the treatment of the negative symptoms of schizophrenia: a double-blind, randomized, placebo-controlled study. International clinical psychopharmacology. 2001, 16, 87–92.

97. Zoccali, R., Muscatello, MR., Cedro, C., Neri, P., La Torre, D., Spina, E., Di Rosa, A.E., Meduri, M. The effect of mirtazapine augmentation of clozapine in the treatment of negative symptoms of schizophrenia: a double-blind, placebo-controlled study. International clinical psychopharmacology 2004;19 (2): 71–76.

98. Schutz, G., Berk, M. Reboxetine add-on therapy to haloperidol in the treatment of schizophrenia: a preliminary, double-blind, randomized, placebo-controlled study. International clinical psychopharmacology. 2001;16: 275–278.

99. Matthews PRL, Horder J, Pearce M. Selective noradrenaline reuptake inhibitors for schizophrenia. Cochrane Database of Systematic Reviews 2018, Issue 1. Art. No.: CD010219. DOI: 10.1002/14651858.CD010219. pub2.

100. Bodkin JA, Siris SG, Bermanzohn PC, Hennen J, Cole JO. Double-blind, placebo-controlled, multicenter trial of selegiline augmentation of antipsychotic medication to treat negative symptoms in outpatients with schizophrenia. Am J Psychiatry 2005;162:388–390.

101. Buchanan RW, Weiner E, Kelly DL, et al. Rasagiline in the Treatment of the Persistent Negative Symptoms of Schizophrenia. Schizophr Bull. 2015;41(4):900-908.

102. Strous RD, Stryjer R, Maayan R, et al: Analysis of clinical symptomatology, extrapyramidal symptoms and neurocognitive dysfunction following dehydroepiandro-sterone (DHEA) administration in olanzapine treated schizophrenia patients: A randomized, double-blind pla-cebo controlled trial. Psychoneuroendocrinology 2007; 32:96–105

103. Ritsner MS: Pregnenolone, Dehidroepiandrosterone, and Schizophrenia: Alterations and Clinical Trials. Neuro-science and Therapeutics 2010; 32-44.

104. Jungerman, T., Rabinowitz, D., Klein, E., 1999. Deprenyl augmentation for treating negative symptoms of schizophrenia: a doubleblind, controlled study. Journal of clinical psychopharmacology. 19, 522–525.

105. Singh V , Singh SP, Chan K. Review and meta-analysis of usage of ginkgo as an adjunct therapy in chronic schizophrenia. International Journal of Neuropsychopharmacology (2010), 13, 257–271.

106. Deutsch, S.I., Rosse, R.B., Schwartz, B.L., Fay-McCarthy, M., Rosenberg, P.B., Fearing, K., 1997. Methylene blue adjuvant therapy of schizophrenia. Clinical neuropharmacology. 20, 357–363.

107. Marchesi, G.F., Santone, G., Cotani, P.,

Giordano, A., Chelli, F., 1995. The therapeutic role of naltrexone in negative symptom schizophrenia. Prog. Neuro-psychopharmacol. 19, 1239–1249.

108. Roesch-Ely, D., Gohring, K., Gruschka, P., Kaiser, S., Pfuller, U., Burlon, M., Weisbrod, M., 2006. Pergolide as adjuvant therapy to amisulpride in the treatment of negative and depressive symptoms in schizophrenia. Pharmacopsychiatry 39, 115–116.

109. DiIorio G, Baroni G, Lorusso M, Montemitro C, Spano MC, and di Giannantonio M. Efficacy of Memantine in Schizophrenic Patients: A Systematic Review. J Amino Acids 2017; 2017: 7021071.

110. Emsley, R., Oosthuizen, P., van Rensburg, S.J. Clinical potential of omega-3 fatty acids in the treatment of schizophrenia. CNS Drugs 2003;17 (15): 1081–1091.

111. Chua, W., DeIzquierdo, S.A.,Kulkarni, J.,Mortimer, A. Estrogen for schizophrenia. Cochrane Database Syst. Rev. 2005. (CD004719).

112. Buchanan RW, Kelly DL, Weiner E, et al. A Randomized Clinical Trial of Oxytocin or Galantamine for the Treatment of Negative Symptoms and Cognitive Impairments in People With Schizophrenia. J Clin Psychopharmacol. 2017;37(4):394-400.

113. Wang J, Zhou Y, Gan H, et al. Efficacy Towards Negative Symptoms and Safety of Repetitive Transcranial Magnetic Stimulation Treatment for Patients with Schizophrenia: A Systematic Review. Shanghai Arch Psychiatry. 2017;29(2):61-76.