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Research Article

Systematic Review of a Series of Home-Grown Studies Concerning Thymoleptics Benefit Re Deficit Syndrome of Schizophrenia

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Abstract

Introduction

Though negative symptoms are a real barricade against effective recovery in schizophrenia, their management by add-on antidepressants has produced changeable consequences. In the current study, some of the local systematic published studies have been the subject of a systematic review, to assess the effectiveness of adjunctive antidepressants on negative symptoms of schizophrenia.

Methods

After probing in identified database, 8 home-based appropriate randomized clinical assessments, containing two hundreds and seventy-seven patients, was nominated. All chosen samples were among the long-lasting patients, with diagnosis of schizophrenia in line with "Diagnostic and Statistical Manual of Mental Disorders", fourth edition, text revision. Following selection, they entered into a series of double-blind trials for random assignment to placebo or an antidepressant, along with their prescribed antipsychotic medicines. In the said trials, the "Scale for Assessment of Negative Symptoms" was the primary scale for evaluation of negative symptoms. Moreover, response was demarcated as a decrease of ⩾20percentage in the score of the said measure (as total item or subscales).

Results

Analysis of "Combined Effect Size" showed a significant positive influence of antidepressant medications on negative symptoms. Similar results, too, were palpable separately with reference to different sub-scales of primary outcome measure. "Anhedonia–Asociality" displayed the best response, followed by "Affective Blunting", "Avolition Apathy", "Attention Deficit", and finally "Alogia". Heterogeneity of the said enquiry was insignificant and acceptable.

Conclusion

Antidepressant drugs have promising sound effects with regard to improvement of negative symptoms of schizophrenia.

Keywords: Deficit Syndrome of Schizophrenia; Negative Symptom of Schizophrenia; Adjuvant Antidepressant Medications; Pharmacotherapy; Serotonergic Antidepressant Drugs; Noradrenergic Antidepressant Drugs

Introduction

Schizophrenia is a heterogeneous syndrome characterized by cognitive, positive, and negative symptoms [1-2]. While positive symptoms talk about new psychological incidents outside of the normal experience (like, delusions and hallucinations,), negative symptoms imply impairment or loss of everyday functions. Negative symptoms include apathy, poverty of speech and thought, anhedonia, blunting of affect, loss of motivation, inattention to social or cognitive input, reduced social drive, and finally lack of social interest [3]. Attentiveness in negative symptoms has

increased quickly over the last years, in parallel with a developing concern in practical and clinical retrieval [4]. Traditionally, negative symptoms are believed to be treatment-resistant and as the major backer to lower functional levels in most patients with schizophrenia, in comparison with their premorbid position [5]. Severe and persistent negative symptoms constitute the deficit syndrome, which is evident in around 25 percent of schizophrenic patients. While amelioration of positive symptoms does not automatically turn into efficient recovery, full functional/social retrieval happens in less than 15 percent of individuals with schizophrenia [6]. An associated impediment is secondary negative symptoms - loss of interest, social drive and expressiveness that results from depression, fear of social stigma, social anxiety, or the extra-pyramidal adverse effects of antipsychotic medications [1]. While negative symptoms are thoroughly connected to the thought deficits, the boundary between negative and cognitive symptoms, as well, is not sharp enough [7]. Schizophrenics do unwell on tests of mental confidence and elasticity, particularly word fluency and the capacity to sustain attention and shift its focus when needed [8]. While debate continues regarding the interconnection and influence of negative vs. cognitive symptoms to functional deficiency, it is recognizable that their impression is considerable [4]. Undoubtedly, the introduction of the antipsychotic medications in the 1950's heralded a novel epoch in the management of schizophrenia. About 70 – 80 % of individuals with schizophrenia who take antipsychotic drug will find that their positive symptoms (delusions and hallucinations) reduce and sometimes may vanish totally [9]. Nevertheless, while antipsychotic drugs are very effective against the positive symptoms, such an operative treatment for the negative symptoms unhappily remains beyond our knowledge [2]. Maybe it is so because the roots of the negative symptoms are more complex than the positive ones and ingrained in psychological factors as in chemical alterations within the brain cells [10]. In the 1980s, the second-generation antipsychotics were introduced and are now the drugs of first choice for treating psychosis [11].

In the beginning, it gave the impression that these new drugs were not only as effective as the first-generation antipsychotic medications in treating the positive symptoms, but they were possibly effective against negative symptoms. But, in fact it was not so. Despite inconsistency in outcomes of published researches, certainly if there is any beneficial effect from the atypical antipsychotics on negative symptoms it is far less striking than their effect on positive symptoms [12]. Some practitioners have used antidepressants in the management of negative symptoms and have claimed that in addition to their effectiveness in combating the depression they may also increase the blood levels of the antipsychotic drugs and hence increase their effectiveness, and not only help with the depressive symptoms but also with the negative symptoms [4,9]. On the other hand, some scholars believe that no one of medications now accessible is an exact management for schizophrenia. All antipsychotic drugs are, approximately, similarly good at subduing psychotic symptoms, and in the same way similarly unsuccessful regarding the amelioration of negative symptoms [13]. Therefore, pharmacotherapy of negative symptoms by supplementary antidepressant medications is not without discrepancy. For example, while scholars like Möller ;[14-18] have faith in helpfulness of adjunctive antidepressants, other researchers like Kissling et al. [19-23] see that an unpredictable, ambiguous or useless approach. Therefore, in the current study and according to our evaluative query (are antidepressant drugs valuable in the management of negative symptoms?), some of the local systematic published studies have been the topic of a new inquiry, to assess over again the efficacy of auxiliary antidepressants on management of negative symptoms of schizophrenia.

Methods

For evaluation, articles in all languages were searched through internet from these databanks: MEDLINE, EMBASE, PsycINFO, LILACS, ISI Web of Science, Cochrane Schizophrenia Group's Specialized Register, The Cochrane Central Register of Controlled Trials, and PubMed. The selection criteria encompassed all home-based, pertinent randomized trials, comparing placebo with antidepressant medications, with reference to amelioration of negative symptoms. In conclusion, 8 studies were designated, which were done during the last 14 years in Razi psychiatric hospital, with a total of 277 male participants [24-30] (Table 1). Unpublished try-outs, non-methodical assessments, open trials, or disciplined estimations by medicines other than antidepressant drugs were excluded from the present study. In the said evaluations the primary analyses were performed in line with the "intention-to-treat", "Last Observation Carried Forward (LOCF) approach". Furthermore, all the cases were chronic schizophrenic inpatients, as accessible sample. Diagnosis of schizophrenia, as well, was in line with the criteria of "Diagnostic and Statistical Manual of Mental Disorders", fourth edition, text revision [31]. In addition, while the studies were carried out consistent with the 'Declaration of Helsinki and Ethical Principles for Medical Research Involving Human Subjects' [32], the patients were educated regarding the procedure, and a signed informed consent was received from those who had in participated in the studies. Duration of at least 2 years of illness, too, was necessary for inclusion of samples. Moreover, cases with co-morbidities such as mental retardation, major depressive disorder, medical problems, and neurological ailments, and cases with diagnosis of schizoaffective disorder or patients, who had been prescribed long-acting depot antipsychotic drug (during the last 6 months) or atypical antipsychotic medications, antidepressant medicines or lithium, were excluded. The "Scale for Assessment of Negative Symptoms" (SANS) [33] was the primary assessment tool for estimation of negative symptoms. Besides, the "Scale for Assessment of Positive Symptoms" (SAPS) [34], "Simpson Angus

Scale" (SAS) [35], "Hamilton Rating Scale for Depression" (HAM-D) [36], and "Mini-Mental Status Examination" (MMSE) [37], were utilized for assessment of confounding parameters. In this regard, SANS, ⩾66, SAPS, ⩾96, and SAS, ⩽10 were the basis of inclusion criteria. In addition, HAM-D and MMSE had been used, for exclusion of depression and cognitive disturbances, separately. So, HAM-D >10 and MMSE <25 were acknowledged as probable depression and cognitive trouble and could cause elimination. After a washout period of one week, patients were prescribed haloperidol (5-10 mg/day), and after that had been randomized to receive either placebo or antidepressant drug, as add-on augmentative maneuvers. For prevention of escalation of psychosis, only the lower dosages of antidepressant preparations were permissible. For preserving blindness of the protocol, all add-on medications were inserted into empty and similar capsules. The surveyor, and personnel, too, was unmindful about the said panel and the nature of medicines set for each group. Patients had been evaluated at starting point and definite intervals by the main and ancillary scales. Also, appraisal of heterogeneity, publication bias analysis and, finally, grading quality of evidence (GRADE) [38], had been performed, on behalf of additional illumination of meta-analysis.

Table 1: Characteristics of involved studies. DB: Double Blind; RCT: Randomized Controlled Trial.

Target Drug	Year of Study	Mode of Study	Technique of Evaluation	Number of Samples
Citalopram [24]	2003	DB	RCT	20
Clomipreamine [24]	2003	DB	RCT	20
Fluoxetine [25]	2004	DB	RCT	48
Nortriptyline [25, 26]	2004	DB	RCT	49
Maprotiline [27, 28]	2005	DB	RCT	20
Fluvoxamine [27, 28]	2005	DB	RCT	20
Reboxetine [29]	2015	DB	RCT	50
Escitalopram [30]	2007	DB	RCT	50

Statistical Analysis

In the present analysis, response was defined as a reduction of ⩾20 percent in the severity of SANS' score (total and subscales). Confidence Interval (CI), Odds Ratio (OR), and combined effect size had been examined for each trial and symptom, independently. Meta-DiSc Version 1.4 [39] and Meta-Essentials Version 1.0 [40] were the statistical software tools for analysis.

Results

While the "Intention-to-treat" analysis was the primary protocol, there was not any significant missing data in the designated surveys. On the word of the outcomes, while the combined effect size of said trials had exposed a significant efficiency as regards the success of antidepressant medications on negative symptoms *(OR = 7.00, CI= 3.79 - 12.93, z= 7.49, p<0.000),* heterogeneity of the present meta-analysis was appropriate (<25%) (Table 2) (Figure 1). Similarly, analogous effects were discernible concerning different sub-scales of SANS, or symptoms of deficit syndrome of schizophrenia, like "Attention Deficit", "Alogia", "Avolition – Apathy", "Anhedonia-Asociality", and "Affective Blunting". In this regard, "Anhedonia–Asociality" exhibited the best response, followed by "Affective Blunting", "Avolition–Apathy", "Attention Deficit", and "Alogia" , in order (Table 3). Heterogeneity of all previously mentioned sub-scales, too, was minimal and thus proper. Based on a domain-based appraisal, because no apparent bias (pertaining to detection, choice, performance, reporting and attrition) was evident, the possibility of bias in this respect was in general small. In addition, the publication bias analysis revealed an adjusted combined effect size=1.95, in comparison with the detected combined effect size=1.76 (variance = 0.19), which, while minimal, does not disregard the requirement for further systematic investigations. Because of randomized trials, palpable directness, acceptable consistency, no serious limitation to study quality, low chance of reporting bias, and shortage of imprecise or sparse data (except than 3 trials with wide confidence intervals), from one hand, and tough indication of association with noteworthy Odds Ratio (>2), based on reliable proof from at least 2 assessments, with no reasonable confounders, Grading Quality of Evidence and Strength of Recommendations (GRADE) for this survey looks helpful and acceptable [38].

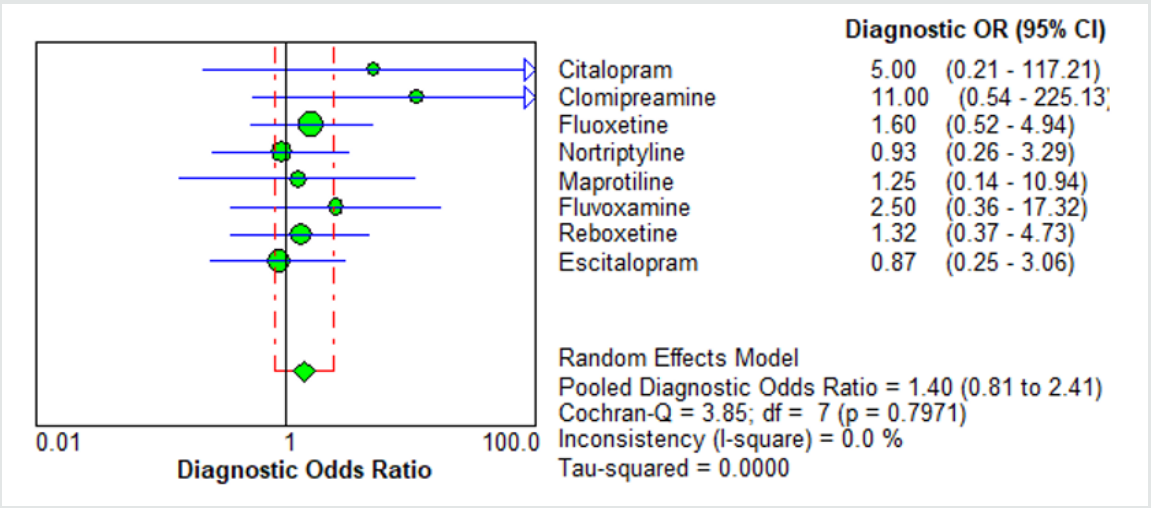

Figure 1: Diagnostic Odds Ratios and pooled Odds Ratio (Random effects model).

Table 2: Overall result of analysis, based on random effects model.

Combined Effect Size	
Odds Ratio	7.00
CI Lower limit	3.79
CI Upper limit	12.93
PI Lower limit	3.79
PI Upper limit	12.93
Z-value	7.49
One-tailed p-value	0.000
Two-tailed p-value	0.000
Number of incl. subjects	277
Number of incl. studies	8
Heterogeneity of meta-analysis model	
Q	5.83
pQ	0.560
I2	0.00%
T^2 (Odds Ratio)	0.00
T (Odds Ratio)	0.00

Table 3: Positive response of various sub-scales of SANS (Pooled Outcome).

Negative Symptoms	Odds Ratio	CI	Z-value	p-value	Heterogeneity (I2)
Anhedonia -Asociality	7.00	3.79,12.93	7.49	0.000	0.00%
Affective Blunting	6.60	3.22,13.53	6.21	0.000	0.00%
Avolition-Apathy	4.77	2.38,9.57	5.31	0.000	0.00%
Attention Deficit	3.74	2.01,6.97	5.02	0.000	0.00%
Alogia	2.57	1.18,5.60	2.86	0.004	15.53%

Discussion

Prevalent occurrence of negative symptoms and their resistance against available treatments, while they denote the most incapacitating and obstinate feature of schizophrenia, make them tough to overlook. Accordingly, interest in negative symptoms resuscitated in the 1980s-90s, with passionate struggles to better comprehend them and manage them more efficiently [41]. So, negative symptoms stay significant since they are the main barricade against a better life for schizophrenic patients [2]. To this

last topic, work focusing on the prodromal phase of schizophrenia specifies that deficit symptoms and cognitive deficiency are evident during the first psychotic breakdown [42], while persistent negative symptoms are recognizable in around 25-30 percent of individuals with long-lasting schizophrenia [43]. Generally, the four major clinical subgroups of negative symptoms are classifiable as affective, communicative, conational, and relational [44]. On the other hand, though deficit syndrome has a main influence on quality of life of the patients [45], they are often linked with an inadequate response to drug treatments [46]. Thus far, studies specially probing negative symptoms in schizophrenia are inadequate [47]. Therefore, proper assortment of therapy of negative symptoms remains a major ignored medical requirement [48], and, according to the diversity of the clinical appearance of schizophrenia, management of negative symptoms, along with therapy for other related symptoms, should be mostly personalized along with a patient's particular physiognomies [49]. Though from 1950s the introduction of operative pharmacological managements for positive symptoms has deliberately moved the diagnostic route to a positive symptom-based model [50], through the 1980s, a quantity of categorizations of schizophrenia based on negative symptoms were presented [51], which exposed, nonetheless, several constraints, comprising the absence of diagnostic steadiness over time and the unfortunate prognostic importance [52]. Back to our discussion and as said by the results of the existent evaluation, antidepressant medications have substantial value for improvement of negative symptoms. Additionally, the highest effect was palpable in regard to "Anhedonia – Asociality", and the least effect had been revealed with reference to "Alogia".

Therefore, our deductions are compatible with Möller [14-16] found antidepressant drugs useful for amelioration of negative symptoms. In addition, it is somewhat compatible with the conclusions of Kissling et al. [19], who found mixture of antipsychotic drugs and antidepressant medications useful in handling negative symptoms, though as said by him the quantity of evidence was too inadequate to let any strong deduction. Incidentally, although they did not find any significant difference between 'leaving the study early due to inefficacy' and 'leaving the study early due to adverse events' between the two treatment groups, contributors treated with the antipsychotic medications in addition to antidepressant prescriptions exhibited, meaningfully, better improvement in negative symptoms than those treated with only antipsychotic drugs. Also, significant difference for the blend therapy was observable in different types of negative symptoms, like "Avolition", "Alogia" and "Affective flattening", which was again comparable to the outcomes of the current evaluation. Similarly, our conclusions were coherent with the outcomes of Rummel et al. [17-18], who found that antidepressants were effective in reducing negative symptoms, with a medium to high effect size, and such a reduction may be at least partially free from the antidepressant influence. In contrary, our deductions are not harmonious with the outcomes of Stahl et al. [20], who indicated that assessment and treatment trials' method for the appraisal of negative symptoms demands more sophistication before therapeutic cheerfulness that superior managements for negative symptoms can be acknowledgeable. In addition, in contrary to our result, which comprised both Serotonin-Specific Reuptake Inhibitors (SSRIs) and tricyclic antidepressants, it is not consonant with Potvin et al. [21], who did not find any significant efficacy as regards the SSRIs. Nevertheless, when their studies were separated in line with the severity of disorder, a moderate and significant effect size appeared for the studies concerning the alleged 'long-lasting patients'. Anyway, along with their conclusion, the accomplished review could not bring any comprehensive backing for the SSRIs. Maybe, as said by Czobor et al., while general effectiveness results appear to be optimistic, evidence for efficacy of present psychopharmacological medicines is hard to evaluate owing to technical difficulties and unstable results [53]. Also, the current evaluation is not in harmony with the outcomes of Hinkelmann et al. [54], who did not find any significant dissimilarity between serotonergic and noradrenergic antidepressants, as augmentative treatment for negative symptoms. Likewise, our results were not consistent with the conclusions of Singh et al. [24], and Fusar-Poli et al. [25], who believed that in spite of usual reportage of helpful responses, most trials often have not used a rigorous standard for description and control of negative symptoms. Thus, the issue of secondary negative symptoms could not be ruled out.

Therefore, efforts for better identification and measurement of negative symptoms should be continued [44]. For example, by studying endophenotypes, experts anticipate to learn how these processes work - not merely in people with schizophrenia, but in other persons who may or may not have a schizophrenia spectrum disorder. As investigation associates subtle signs and symptoms of illness to an individual's basic genetic character, a better understanding of this range of ailments will be imaginable in near future [55]. However, the mechanism by which addition of antidepressant medications to antipsychotic drugs may cause lessening of negative symptoms is still vague [45]. More recently, the National Institute of Mental Health (NIMH) Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) twisted its care to negative symptoms. From a therapeutic standpoint, it is notable that the MATRICS consensus statement makes reference to stubborn negative symptoms and designates that the distinction between primary and secondary negative symptoms is not indispensable [7], which is many times unachievable [56-59]. Surely, restricted quantity of systematic native studies, short-term period of evaluations, gender-based sampling, and diverse sampling sizes were among the weaknesses of the current study, which together may limit the generalizability of the findings.

Conclusion

Antidepressant drugs have promising sound effects with regard to improvement of negative symptoms of schizophrenia.

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