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OMEGA-3 & OLANZAPINE AUGMENTATION IMPLICATIONS TO COMBAT THE SCHIZOPHRENIA SYNDROMES; A CASE STUDY AT NISHTAR MEDICAL UNIVERSITY MULTAN.

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ABSTRACT

Schizophrenia is the leading cause of disability worldwide and individuals have significantly lower life expectancy, higher rates of suicide and higher prevalence of chronic health conditions when compared to the general population. Regarding treatment strategies along with rehabilitation services, many patients responded well to antipsychotic drugs. This study was conducted to investigate the Omega-3 Fatty Acids along with Olanzapine Augmentation potential benefits. A randomized controlled study design was adapted as inclusive criteria for schizophrenia patients with adjusted Olanzapine doses. The sample size was (N=45) including 30 schizophrenia patients while 15 individuals were healthy but prone to stress and this treatment lasts for six months with regular follow up. Olanzapine treatment was given to 15 out of 30 individuals while rest of the patients was treated with Olanzapine along with Omega-3(Ω-3) fatty acids. The stress prone individuals were also treated with Ω-3 fatty acid therapy. Positive and Negative Syndrome (PANSS) scale was used as assessment tool. The follow up interval was Four weeks up to six months for each group and results indicated that the group with adjusted Olanzapine doses didn't express any deterioration in Schizophrenia symptoms and remain static, while the group with Olanzapine + Ω-3 fatty acid therapy exhibited significant improvements in all Schizophrenia symptoms. The 3rd/ Control group individuals with stress indicated satisfactory response by improvement in overall symptoms as positive and negative symptoms were taken to be absent in them. PANSS total scores of Olanzapine & Olanzapine + Ω-3 fatty acid therapy were compared. PANSS test scores for Olanzapine + Ω-3 fatty acid therapy indicated the significant improvement in Schizophrenia symptoms. Our findings provide the evidence for the potential therapeutic effects of Ω-3 fatty acid as an adjunct treatment to olanzapine in Schizophrenia symptoms management. However, this is one of the Preliminary study on Schizophrenia symptoms management, further studies are suggested for better insight

Key Words: Schizophrenia, Olanzapine, Ω-3fatty acids, Cognitive symptoms, Antipsychotic Drugs, PANSS Scale, Olanzapine + Ω-3 fatty acid.

Introduction.

Schizophrenia, a severe chronic mental condition, impacts around 1 % of the global population [1]. It is marked by euphoric emotions, including hallucinations and delusions, unpleasant symptoms such as depression, Alogia, Avolition, considerable behavioral problems, and cognitive impairments like diminished psychological functions [2]. The schizophrenia origin is not still understood well. The variety of indications proposes that the schizophrenia etiology is complex and involves both environmental & genetic factors like prenatal infection as well as maternal malnourishment [3]. Schizophrenia is not caused due to a single gene instead studies on identical twins demonstrated that the hereditary variables contribute just 50% to the risk rates. Individuals with defective genes may exhibit increased susceptibility to numerous environmental risk factors; consequently leading to illness development [4]. The defective genes may enhance the Schizophrenia susceptibility in an individual by numerous environmental risk factors, consequently leading to the development of disorder [4]. Schizophrenia often onset in late adolescence corresponds with disruptions in brain development and myelination processes. Aberrant development of brain during the prenatal or prompt postnatal age leads to functional impairments, proposing the harmful central nervous system (CNS) variables might substantially influence the advancement of the syndrome. The schizophrenia Patients demonstrate a substantial diminution in total grey & white matter density and volume in brain compared to healthy people, accompanied by a marked enlargement of the lateral & 3rd ventricles [5, 6].Structural changes in the brain gradually manifest before the onset of psychosis in those at ultra-high risk (UHR), generally occurring in early adult-hood or late-adolescence & continue throughout the patients' lifespan [7–12]. Cerebral abnormalities were identified in chronic schizophrenia postmortem inspections and were confined to particular regions, such as temporal lobe, amygdala, cerebellum, medial temporal lobe, basal ganglia, superior temporal gyrus, corpus callosum, thalamus and inferior parietal lobule [13]. The absence of such deformities in un-affected siblings & healthy persons suggests that these structural anomalies of brain are expected to link this disorder. Schizophrenia is considered a psychological disorder since the human brain governs all activities and actions. To improve understanding of the genesis of such disease, neurobiology & biochemistry of schizophrenia brains was focused to detect these changes. Brain contains highest lipid content as 50% of its dry weight consists of lipids and the % of Phospholipids in overall lipids membranes is about more than 60%. There are 2 polyunsaturated fatty acids families which constitute Brain phospholipids Omega-3 & Omega-6. The brain contains 40% of Docosa Hexaenoic Acid (DHA) as entire membrane phosphor-lipid fatty acids. DHA is vital for typical brain development & plays a dynamic role in numerous biological progressions, including receptor-binding, Neuro-transmission, signal-transduction & cognitive roles including learning & memory [14–16].The phosphor-lipids & poly-unsaturated fatty acids equilibrium of brain in schizophrenia patients is a vital research focus to clarify the link among certain lipid-molecules & the structural and functional variations of brain. A technique to obstruct the advancement and progression of such disorder could be developed. Horrobin [17] put up Phospholipid-Hypothesis on Schizophrenia. The theory emphasizes that eminent activity of phospholipase-A2 (PLA2) in Schizophrenia patients, which discharges PUFAs, specifically DHA & AA, from phospholipid membranes, led to shortage of PUFA and advanced brain tissues decline. That led to a typical Neurotransmission, psychosocial manifestations & impairments in mental and cerebral processes. Evidence demonstrated a notable decrease in PUFAs, specifically AA & DHA, in the peripheral-blood (erythrocyte & plasma membranes) of schizophrenia patients [18–30]. The substantial decline in the levels of DHA & AA was confirmed by two Meta analyses in the patients of schizophrenia with and without antipsychotic treatment [27, 33]. Different studies demonstrated that there were no discrepancies or even elevation in AA & DHA levels in the individuals with schizophrenia, relative to healthy people. Medema et al. (2016) report that 61.9% of patients were administered atypical antipsychotic medicine, recognized for its ability to enhance the synthesis of polyunsaturated fatty acids (PUFAs) and elevate PUFA concentrations [34]. Reports indicate a substantial degradation of phospholipids and a decrease in DHA inside the brain's orbitofrontal cortex (Brodmann area 10, BA10), suggesting the deficiency of DHA in the brain is linked to the onset of

schizophrenia [35–37]. Reports indicate no significant differences in DHA levels throughout several brain regions, including the amygdala and prefrontal cortex, between individuals with schizophrenia and control subjects. This suggests that variations in PUFA levels may be exclusive to different locations. The absence of comparable abnormalities in unaffected siblings and healthy controls suggests that the identified structural brain anomalies in patients are likely associated with the disorder itself [8, 12]. The main symptoms of schizophrenia are categorized into positive, negative, and cognitive symptoms. Positive symptoms include hallucinations and delusions, while negative symptoms encompass blunted emotions, difficulty experiencing pleasure, and cognitive symptoms involve attention deficits. This study examines the genesis of brain PUFA deficiency in patients, the role of PUFAs in the advancement of this disorder, and the beneficial effects of Omega-3 Fatty Acids supplementation. This study aimed to examine the symptoms and cognitive functioning, investigating the potential mechanisms of Omega-3 Fatty Acids that contribute to the beneficial effects to combat schizophrenia symptoms.

Research Objectives

Enhancing underprivileged people's access to omega-3 fatty acids to maximize their advantages in the treatment of mental health issues and disorders like schizophrenia. Furthermore, enhancing understanding of the significance of omega-3 fatty acids in mitigating the risk of diabetes, infertility, and weight gain may result in improved health outcomes. This study aims to address the intact research field by elucidating the significance of omega-3 fatty acids in mental health therapy, hence facilitating future research and treatments.

Material method

Schizophrenia is a complicated neuropsychiatric condition characterized by symptoms such as hallucinations, delusions, emotional blunting, and apathy towards one's environment. PANSS Scale is frequently utilized when assessing the efficacy of antipsychotic therapies for Positive and Negative Syndromes of Schizophrenia. The PANSS rating system allows physicians to distinguish among positive & negative symptoms, hence enhancing diagnostic and prognostic accuracy. Antipsychotic drugs efficiently control positive symptoms; however, negative symptoms are less responsive to therapy and frequently result in long-term morbidity & functional deficits in patients with schizophrenia. The PANSS scale, created by Victor Peralta and Manuel J. Cuesta in 1994, separately evaluates positive & negative symptoms, enabling investigators to quantify and track their severity. Its reliability and validity have established it as a prevalent instrument in research contexts (Journal of Addiction Research and Therapy 8, 2017 by Suneta Kumari, Mansoor Malik, Christina Florival, Partan Manalai). Sofia Papa performed research in 2023 to evaluate the effectiveness of antipsychotic drugs in alleviating pessimistic symptoms, employing the Positive and Negative Syndrome Scale (PANSS). This evaluation instrument has 30 items, each accompanied by a specific description & a 7-point rating scale ranging from 1 to 7, signifying absence to extreme presence. The PANSS is a thoroughly established tool for assessing symptoms of schizophrenia, including positive, negative, and psychopathological aspects. This interview-based evaluation assesses the presence and severity of both positive and negative symptoms, as well as overall psychopathology in persons with schizophrenia. The 30 items were categorized into 3 subclasses: 7 exhibited positive symptoms, 7 displayed negative symptoms, and 16 encompassed general psychopathological symptoms. The severity of symptoms was assessed using a 7-point scale, with likely ranges of 7-49 for both positive and negative scales, and 16-112 for general psychopathological manifestations. The dominance of one condition relative to another can be assessed by bipolar indexing, which produces a spectrum from -42 to +42.

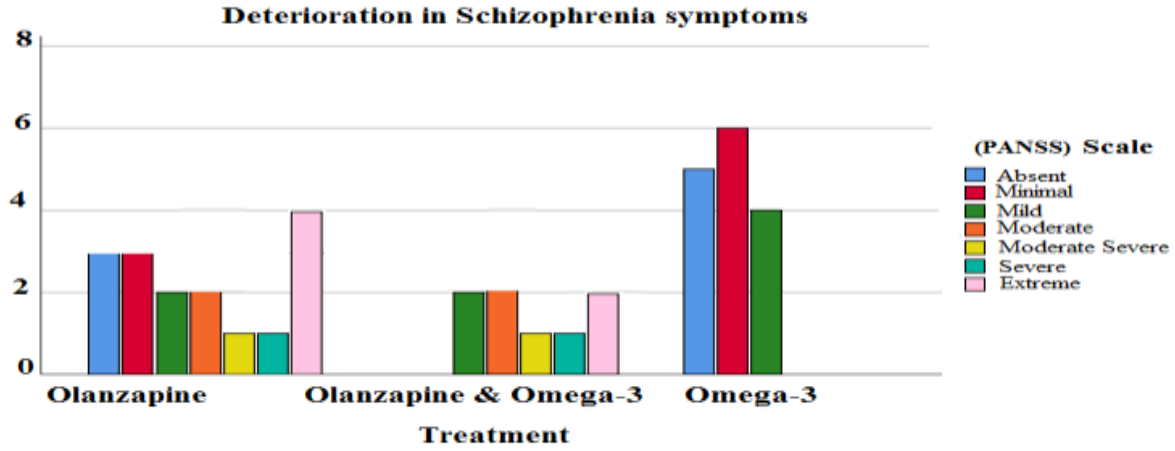
Results

A paired t-test was adopted for this comparative analysis. All three groups underwent analysis of the 30 characteristics of the PANSS scale. Data analysis for the initial group with Olanzapine treatment

indicated that all parameters were steady, with no deterioration of symptoms. The second group having Olanzapine + Omega-3 Fatty Acid treatment exhibited notable enhancements in 7 out of 30 parameters (P2, P3, N1, N2, N3). The third group of individuals which were prone to stress indicated significant efficacy in fostering mental well-being in healthy persons, improving mood and alleviating stress and sadness.

Medication Tabulation for Schizophrenia Positive and Negative Syndrome

										Total
			Absent	minimal	mild	moderate	moderate severe	severe	extreme	
MEDICATION	Olanzapine	Count	10	4	1	0	0	0	0	15
		MEDICATION	66.7%	26.7%	6.7%	0.0%	0.0%	0.0%	0.0%	100.0 %
	Olanzapine and Omega 3	Count	0	0	0	8	1	3	3	15
		MEDICATION	0.0%	0.0%	0.0%	53.3%	6.7%	20.0%	20.0%	100.0 %
	Omega 3	Count	8	4	3	0	0	0	0	15
		MEDICATION	53.3%	26.7%	20.0 %	0.0%	0.0%	0.0%	0.0%	100.0 %
Total		Count	18	18	8	4	8	1	3	3
		MEDICATION	40.0 %	40.0%	17.8 %	8.9%	17.8%	2.2%	6.7%	6.7%



The control group had substantial responses to omega-3 fatty acids in parameters P3, P6, P7, N3, N4, and all G. Post-hoc Tukey test findings indicated significance in individuals administered both olanzapine and omega-3 fatty acids, as well as in those getting omega-3 fatty acids only.

Dependent Variable: Before Values

			Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
	(I) Before Treatments	(J) Before Treatments				Lower Bound	Upper Bound
LSD	1	2	-1.00000	3.67402	.786	-8.2676	6.2676
		3	-19.97778*	3.67402	.009	-27.2454	-12.7102
	2	1	1.00000	3.67402	.786	-6.2676	8.2676
		3	-18.97778*	3.67402	.000	-26.2454	-11.7102
	3	1	19.97778*	3.67402	.000	12.7102	27.2454
		2	18.97778*	3.67402	.000	11.7102	26.2454

ANOVA

Before Values

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	165.644	2	82.822	.588	.557
Within Groups	18595.289	132	140.873		
Total	18760.933	134			

ANOVA

After Values

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	11404.015	2	5702.007	18.774	.000
Within Groups	40090.400	132	303.715		

Multiple Comparisons

- The significant value for Mean difference is 0.05.

Discussion.

The incidence of mental health disorders is increasing daily, profoundly affecting our lives, cognitive processes, interpersonal interactions, emotions, and overall wellness. Negative social, environmental, economic, and emotional variables lead to the onset of mental diseases. A variety of mental health illnesses are present, encompassing anxiety, depression, and bipolar disorder. Schizophrenia, a severe, persistent, and intricate mental health disorder, is an increasing worry that several psychiatrists face in their clinical practice. This incapacitating disorder impacts individuals' cognition, emotions, and actions, resulting in considerable discomfort. Positive symptoms consist of delusions, hallucinations, aggression, and grandiosity, whereas negative symptoms involve social and emotional retreat, communication challenges, and cognitive deficits. Common psychopathological characteristics encompass tension, anxiety, guilt, noncompliance, and social isolation. The Positive and Negative Syndrome Scale (PANSS) is a diagnostic instrument utilized to evaluate the effectiveness of therapies for schizophrenia and other psychiatric disorders. The integration of psychotherapy, rehabilitative services, and atypical antipsychotics such as olanzapine has demonstrated efficacy, attributed to its comparatively low occurrence of extrapyramidal side effects. Olanzapine's mode of action includes the modulation of both dopamine and serotonin receptors. Nonetheless, it also presents several detrimental consequences, such as weight gain, which heightens the chance of developing diabetes mellitus and infertility. Conversely, omega-3 fatty acids, which are needed and not synthesized by the body, provide many advantages when acquired from supplementation or dietary sources such as fish

(tuna, salmon, trout), seeds (flax, rapeseed, walnut, chia, hemp), and soybean oil. These polyunsaturated fatty acids possess anti-inflammatory characteristics, enhance immunological function, and promote brain function and development. Furthermore, they are abundant in calcium, enhancing bone health and diminishing the risk of osteoporosis and arthritis. Omega-3 fatty acids provide a strong anti-inflammatory effect that aids in the treatment and prevention of several mental diseases. This study sought to investigate the efficacy of omega-3 fatty acids in improving schizophrenia therapy and reducing the side effects linked to atypical antipsychotics such as olanzapine. This research sought to highlight the significant advantages of essential fatty acids, which warrant consideration for daily supplementation. The increasing incidence of mental health issues and psychosis, along with the advantageous properties of these fatty acids, renders them a superior therapeutic alternative for psychiatric illnesses. Outpatient department patients with schizophrenia were chosen for this investigation. A sample of 45 individuals was selected, consisting of 15 men and 15 females diagnosed with schizophrenia, without any history of comorbidities, aged between 18 and 45 years. From January 2023 to June 2023, one group was administered 10mg of olanzapine orally once daily, accompanied by routine follow-ups every four weeks for duration of six months. A other cohort, fulfilling identical requirements, was administered 10mg of olanzapine orally once daily, in conjunction with 500mg of omega-3 fatty acids (Cap Normega) twice daily, accompanied by routine four-week follow-ups for a duration of six months. Both groups were evaluated with the Positive and Negative Syndrome Scale (PANSS) scoring system**.** Furthermore, 15 individuals were chosen who lacked a schizophrenia diagnosis yet experienced stress and anxiety that substantially affected their everyday activities. This cohort, sharing the same age range and lacking a history of comorbidities, was administered Cap Normega at an identical dose. They were observed every four weeks for duration of six months. The results, evaluated by the paired t-test, were compelling. The initial cohort, administered olanzapine alone, had little or statistically insignificant enhancements in symptoms as evaluated by the PANSS scale. Although the conventional drug, utilized for decades, did not worse problems, it was unexpected to observe minimum or no enhancements. Significantly, 7 of 15 female patients exhibited weight increase (as reported by Eric Prommer, MD, in April 2012), while negative and other pathophysiological characteristics were steady, without deterioration. The second group, administered olanzapine and omega-3 fatty acids for six months with consistent four-week follow-ups, produced significant benefits. Utilizing the PANSS scale, notable enhancements were noted in positive symptoms (P2, P3, N1, N2, N3) and overall pathophysiological characteristics. This group did not exhibit substantial weight increase, aligning with Amyrichper's results (January 2023), which emphasized the advantages of omega-3 fatty acids in enhancing brain health and alleviating chronic mental problems. Mei-Chi Hsu, Young-Sheng Huang, and Wen-Sheng OuYang (2020) similarly demonstrated that omega-3 fatty acid supplementation diminished the conversion rate to psychosis and enhanced both positive and negative symptoms, resulting in significant overall improvement in schizophrenia patients. My research revealed that 21 of the 30 PANSS scoring factors exhibited significant outcomes, but 9 parameters did not demonstrate significant responses, underscoring the essential function of omega-3 fatty acids in mental and mood disorders, as previously shown by Malcom Peet (2008). In contrast to prior research that utilized meta-analysis and molecular-level methodologies with vast sample sizes, my work presents a unique viewpoint. The third group, consisting of 15 patients without a history of schizophrenia, was administered just omega-3 fatty acids as a placebo. They demonstrated exceptional outcomes. As they did not exhibit schizophrenia, their positive and negative symptom scores were negligible or nonexistent. Nevertheless, the findings indicated substantial enhancements in negative symptoms (N3, N4) and overall pathophysiological characteristics (G). Of the 30 characteristics, 19 exhibited significant outcomes; corroborating Urvi Dalal's findings (2021) that omega-3 fatty acids offer distinctive features that invigorate our bodies and enhance our mood.

CONCLUSION

In conclusion, Omega-3 fatty acids have developed as an essential element in the treatment of schizophrenia, a persistent and devastating mental health disorder that is increasingly impacting young adults. Although antipsychotic medicines are fundamental to treatment, their combination with omega-3 fatty acids has been found to alleviate symptoms and mitigate the detrimental effects of these treatments, as evidenced by this study. Furthermore, these vital fatty acids have demonstrated significant efficacy in fostering mental well-being in healthy persons, improving mood and alleviating stress and sadness.

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