A COMPARATIVE STUDY OF EFFICACY AND SAFETY PROFILE OFACETYL-L-CARNITINE AS AN ADD-ON THERAPY IN THE TREATMENTOF DEPRESSION

Dissertation submitted to

THE TAMILNADU DR.MGR MEDICAL UNIVERSITY

CHENNAI

In partial fulfilment of the regulations

For the award of the degree of

M.D. PHARMACOLOGY

Branch VI

Reg.No: 201816151

GOVT. KILPAUK MEDICAL COLLEGE AND HOSPITAL

CHENNAI-10

MAY 2021

CERTIFICATE

This is to certify that this dissertation titled "**A COMPARATIVE STUDY OF EFFICACY AND SAFETY PROFILE OF ACETYL-L-CARNITINE AS AN ADD-ON THERAPY IN THE TREATMENT OF DEPRESSION**" is the bonafide original work done by **Dr.NILOFER NOORIE.M,** Post graduate in Pharmacology, under my overall supervision in the Department of Pharmacology, Govt. Kilpauk Medical College and Hospital, Chennai, in partial fulfilment of the regulations of the TamilnaduDr.M.G.R. Medical University for the award of **M.D. Degree** in **Pharmacology (Branch VI).**

Dr. T. ARUNA, M.D.,
Professor & HOD
Department of Pharmacology
Govt. Kilpauk Medical College and Hospital,
Chennai – 10.

Dr. VASANTHAMANI
M.D,DGO,MNAMS,DCPSY,MBA
The Dean,
Govt. Kilpauk Medical College and
Hospital, Chennai-10.

CERTIFICATE

This is to certify that this dissertation titled "**A COMPARATIVE STUDY OF EFFICACY AND SAFETY PROFILE OF ACETYL-L-CARNITINE AS AN ADD-ON THERAPY IN THE TREATMENT OF DEPRESSION**" is the bonafide original work done by **Dr.NILOFER NOORIE.M,** Post graduate in Pharmacology, under my guidance in the Department of Pharmacology, Govt. Kilpauk Medical College and Hospital, Chennai, in partial fulfilment of the regulations of the TamilnaduDr.M.G.R. Medical University for the award of **M.D. Degree** in **Pharmacology (Branch VI).**

Dr. T.ARUNA, M.D.,Professor
(Guide)
Departmentof Pharmacology
Govt. Kilpauk Medical College
and Hospital , Chennai – 600010.

DECLARATION

I solemnly declare that this dissertation titled "**A COMPARATIVE STUDY OF EFFICACY AND SAFETY PROFILE OF ACETYL-L-CARNITINE AS AN ADD-ON THERAPY IN THE TREATMENT OF DEPRESSION**", is the bonafide work done by me at the Department of Pharmacology, Govt. Kilpauk Medical College and Hospital, Chennai, under the supervision of Dr.ARUNA.T,M.D., Professor, Dr.G.CHENTHAMARAI, M.D., Associate Professor, Department of Pharmacology, and Dr.M.MALAIAPPAN, M.D, Professor and Head of Department of Psychiatry, Govt. Kilpauk Medical College and Hospital, Chennai. This dissertation is submitted to The TamilnaduDr.M.G.R. Medical University, Chennai in partial fulfilment of the University regulations for the award of Degree of M.D.Pharmacology (Branch VI) examinations to be held in May 2021.

Place : Chennai

Date :

Dr.NILOFER NOORIE.M

ACKNOWLEDGEMENT

I thank God, the Almighty for His countless blessings and granting me the capability for this success.

My deepest gratitude to the patients who willingly participated in this study without them, this would have never been accomplished.

I sincerely thank,**Dr.VASANTHAMANI, M.D., D.G.O, MNAMS, DCPSY, MBA,**Dean, Government Kilpauk Medical College and Hospital for permitting me to use institution resources for the research project.

I would like to extend my sincere gratitude to **Dr.ARUNA.T, M.D.,**Professor, Department of Pharmacology, Govt. Kilpauk Medical College and Hospital, for guiding me with her contagious enthusiasm and dynamism throughout my course. Her dedication, meticulous scrutiny and scholarly advice have enabled me to complete my thesis.

My wholehearted thanks to my mentor **Dr.C.RAMACHANDRA BHAT, M.D.,** Professor and HOD, Department of Pharmacology, Govt. Kilpauk Medical College and Hospital,whose wisdom,knowledge and commitment for research and teaching has motivated me to perform better throughout my post graduation.

My heartfelt gratitude to my Co-Guide , **DR.G.CHENTHAMARAI**Associate professor, Department of Pharmacology, Govt. Kilpauk Medical College and Hospital, who have been nothing but an

inspiration. I thank her for being a constant source of encouragement and support ,not only in this study but in all my professional endeavors.

I extend my thanks to **Dr.K.MalarSivaraman, M.D.,**Professor, Department of Pharmacology, Govt. Kilpauk Medical College and Hospital for her thoughtful insights and knowledge that contributed to this thesis.

My special thanks to the following facultyfor their timely suggestions and insights, **Dr.Keerthanabrattiya,M.D;Dr.Jeyasudha,M.D; Dr.Rajeshkumar,M.D; Dr.Sasikala,M.D; Dr.Bhuveneshwari,MD**;Assistant Professors, Department of Pharmacology, Govt. Kilpauk Medical College.

I owe special thanks to **Dr.RoshanPraburaj**and**Dr.Soundarapandian**my lovely colleagues and friends for moving mountains for me in the way of completing this thesis. No words would describe the help ,patience and support for me.

I sincerely thank **Dr.J.Mahalakshmi**, for her unfailing trust and love throughout my entire course and research work. And also I thank my junior and senior colleagues, Dr.Kavitha, Dr.Vijayabhanu,Dr.Praveena,Dr.Jayapriya and Dr,Arunkumar for their encouragement and timely help .

I owe my earnest gratitude to my parents**Mrs.SalamathNisha** and**Mr.MohamedYousuf**, who endlessly have loved, supported, trusted my abilities and motivated me to be who I am today. I mention my special thanks to my dear friend **Dr.Jwalamukhi**, for always being there and supporting me

through this entire process. And I also thank my brothers **Nihath**and **Noufar**for always standing by me. I appreciate all your patience and support during my post graduate studies.

I dedicate the thesis to my adorable daughters **Nazaara** and **Shazana**who are the pride and joy of my life, Thank you for being YOU darlings.

At last,but not the least I do not know how to begin thanking you, **Dr.Shameer** my dearest husband and a best friend who have always been there for me. You have tolerated and cheered me up during my tantrums with a smile, and always have inspired me to be myself. You are a true blessing from God.

Dr.NILOFER NOORIE.M

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

5HIAA – 5-Hydroindoleacetic acid

5HT – Serotonin

5HTT – Serotonin transporter

ACC – Anterior cingulated cortex

ALCAR – Acetyl-L-Carnitine

BDNF – Brain derived neurotropic factor

CBT – Cognitive behavioural therapy

CREB – cAMP responsive element binding

CRF – Case Report Form

DALYs – Disability adjusted life years

DSM – Diagnostics & Statistical Manual of mental disorder

ECT – Electro convulsive therapy

HAM-D – Hamilton Depression Rating Scale

HDMS – Hamilton Depression & Melancholia Scale

HPA – Hypothalamo pituitary axis

ICD – International Classification of Diseases

MADRS – Montgomery Asberg Depression Rating scale

MAO – Monoamine oxidase

MDD – Major Depressive Disorder

mGlut – metabotropic glutamate

NAc – NucluesAccumbens

NE – Norepinephrine

NF-κB – Nuclear factor kappa B protein

NMDA – N-methyl-D-aspartate

PFC – Prefrontal cortex

SNRI – Serotonin \norepinephrine reuptake inhibitor

SSRI – Selective serotonin reuptake inhibitor

TCA – Tricyclic antidepressant

TMS – Transcranial magnetic stimulator

YLDs – Years lived with disability

INTRODUCTION

Depression is one of the largest silent epidemics worldwide and it is a compelling public health concern. It is one of the major causes of disability with more than 264 million people affected worldwide. It is one of the leading contributor to overall global burden diseases(1). Depression due to its high prevalence, morbidity, economic burden and social stigma isconsidered as a major public health disorder. The global disease burden estimated the prevalence of unipolar depression is 5.8% in men and 9.5% in women. It has been estimated that it would be the second leading cause of disability – adjusted life years DALYs by 2020(2). Thereby worldwide prevention and management of this disease has become essential in present time.

Depressive disorder is a blanket term enclosing major depressive disorder, dysthymia , disruptive mood dysregulation, substance/medication-induced depressive disorder, premenstrual dysphoric disorder and depressive disorder due to another medical condition(2). Symptoms of the depressive disorders are common ie.,low mood, irritability, loss of appetite with somatic and cognitive features which have a huge impact on the functioning capability of the individual. The differentiating aspect in the spectrum of disorders is the time, duration of symptoms or episodes and the diagnosed etiology.

Over the past 50 years, only a few drugs are used for the treatment of depressive disorders have distinctive therapeutic efficacy. Two-thirds of patients do not achieve full remission of symptoms on current available antidepressants(3). Moreover the therapeutic effect is seen only after 2-3 weeks of antidepressant treatment in those who achieve adequate remission , thereby increasing the risk for complications such as suicide(4). This delay in the onset of remission had been a major driving factor to develop novel therapeutics with rapid effects.

Recent researches on Acetyl-L-Carnitine (ALCAR) shows an antidepressant effect in few animal and human studies. It is an oral dietary supplement that acts by acetylating protein targets and modulating their function. ALCAR is reported to be well tolerated and can readily cross the blood brain barrier (5). Standard Antidepressants like Clomipramine following an intraperitoneal administration in rodents takes 2-3 weeks for its therapeutic effect whereas ALCAR exhibits anti depressant effect within 2-3 days. Although ALCAR is non-specific and can target numerous biological pathways it is found to provide a rapid antidepressant response by acetylation of histone proteins that control the BDNF transcription and metabotropic glutamate 2(mGlut 2) receptors in hippocampus and prefrontal cortex (PFC). ALCAR is noted to exhibits anti depressant efficacy in genetic rat susceptibility model and chronic stress exposure animal model ,whichclosely mimics depression in humans(6).

Many researchers suggest that chronic stress reprograms the gene expression in certain areas of brain such as the Hippocampus and Nucleus Accumbens (NAc) and correcting the post translational modifications of histones can normalize the gene transcription which leads to anti depressant responses(7). Histone deacetylase inhibitors given either intraperitoneally or directly into hippocampus, NAc and amygdale promote the anti depressant response following stress exposure (8). Similar mechanism has been suggested for ALCAR where it increases histone acetylation and normalization of BDNF or mGlu2 in hippocampus and PFC promoting resilience following chronic stress in rodents.

Research also shows that normalization of mGlu2 receptor expression through an epigenetic mechanism is related functionally to anti depressant responses. Also ALCAR showed limited antidepressant efficacy in mGlu2 knockout mice(9).

An endogenously produced acetyl-l- carnitine function is important in multiple behavioral domains. Significant reduction of acetyl-l- carnitine has been associated with glutamatergic dysfunction of dendritic plasticity abnormality in multiple brain regions(10). Various studies indicate that fatty acid and lipid metabolism alterations are salient factor for neuroplasticity that occurs in patients with depression(11). In the prospect,carnitine is a potential substance with antidepressant effects which is known to modulate the neutrotropic activity in nervous tissues. The higher concentrations of the

carnitine is in the form of acetyl-L-carnitine prevents excessive neuronal death(9).

Recently, the inhibition of proliferation of neuronal progenitor cells in the dentate gyrus of hippocampus is proposed to be a central pathogenic element of depression. ALCAR has significant concentration dependant hippocampal neurogenic activity by producing differentiation of stem cells / hippocampal adult progenitor to mature neurons(12). The beneficial effects of ALCAR in depression are supported by numerous preclinical studies in animal and cellular models.Therefore anti-depressant effect of acetyl –L-carnitine makes potential agent in the treatment and management of depression.

There are only few clinical trials that have proved the efficacy of ALCAR as a rapid acting anti-depressant. Additionally there are no studies in Indian population to demonstrate this beneficial effect of ALCAR. Hence, this study is undertaken as an open label prospective interventional study to assess the therapeutic effect of ALCAR as an add-on therapy to SSRIs in the treatment of Depression and its effectiveness in reducing the latency period of anti-depressant effect.

REVIEW OF LITREATURE

Depression is defined as a common mental disorder, characterized by Sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feeling of tiredness, and poor concentration, for at least two weeks".

According to WHO, depression can be a longterm health issue or recurrent in nature, which ultimately leads to impaired ability of the individual to perform in school, work or manage with day to day activities, also in its severe form depression ends up in suicide.

Depressive disorders majorly include 2 main sub types are,

1. **Major depressive episode** - which manifests as depressed mood, loss of interest, unable to enjoy pleasure and decreased energy,depending upon the severity it can be graded as mild, moderate or severe.

2.**Dysthymia** - is a chronic or persistent form of mild depression, the symptoms are more like depressive episode but less intense(13).

EPIDEMIOLOGY

GLOBAL BURDEN

As per WHO, depression is ranked fourth leading cause of disability globally. Its estimated that in 2020 depression will raise to become second leading cause of disability(14). Depression is the most prevalent of all

psychiatric disorders. Over 300 million population have been affected around the world, which makes it about 4.4% of the world's population. The prevalence of depression has increased at an alarming rate of 18% from 2005 to 2015(13). Globally in 2015, major depressive disorder has caused fifty million years lived with disability (YLD) where the countries with low income and middle income exhibited higher occurrence of about 80% of depressive disorders. Of all the non fatal disease ,major depressive disorder alone contributes to 7.5% of total years lived with disability(13).

Depression – prevalence in South East Asia and India

WHO estimated that in India 4.5% of the total population has been diagnosed with major depressive disorder. Also depressive disorders are major health burden which is about 7.1% of total YLD.(13) Depressive disorders were about 46.5% in patients attending primary health care facilities as per the study done in Goa.

The prevalence of depressive disorders was higher than expected in many epidemiological studies done in various regions of Tamilnadu. In a study in Tamilnadu prevalence of MDD in women aged from 18 to 45 years was 20%. Depression among elderly of south Indian rural areas was estimated to be 9.3% in a community based study which revealed the significant burden of the disease in the community.

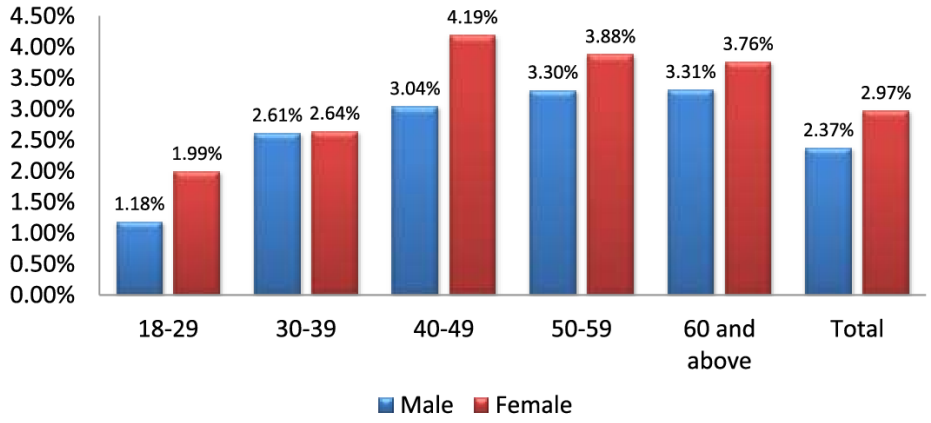

Figure 1:Prevalence Of Depressive Disorders In India By Age &Sex - National Mental Health Survey(NMHS) 2015-2016

A recent study in south Indian population showed the overall prevalence of depression to be 15.1%.(15). The neuropsychiatric diseases in south east Asian regions are 11% of the Disability adjusted life years (DALY) and 27% of YLDS. An epidemiological analysis revealed that there is 26.3% prevalence of depressive disorder in primary care in these regions. Among which 23 % report health issues that are severe to be a crippling disease. Impairment in inter personal and occupation in terms of cost by lost work is also higher in patients with depressive disorder(16).

NEUROANATOMY OF DEPRESSION:

According to researchers, there is a difference between the brains of the normal people and people with depressive disorders. Although there is no clear evidence , the hippocampus to plays a role in the development of depression , hippocampus is observed to be smaller with lesser serotoninergic receptors in patients with major depressive disorder(17). In clinical depression and animal models of stress induced depression, hippocampus is observed to be atrophied with reduced functional integrity. There is a down regulation of 5HT1A

receptors and neurogenesis in hippocampus and area of dentate gyrus in animal models of depression whereas there is an increased expression of these receptors in normal hippocampus and dentate gyrus(15).

In order to study the pathogenesis involved in major depressive disorder numerous neuroanatomical studies have explored the human brain which connects the ventero medial and dorso lateral sectors of pre frontal cortex as main substrates of neural dysfunction. A study connected the functional connectivity of anterior cingulated cortex (ACC) sub regions namely, pregenual ACC (PGACC) and anterior subgenualACC(SGACC)with the severity of depression . The connectivity in these areas determines the severity of depression. Also these sub regions of ACC are involved in the subclinical depression(18).

Hippocampal volume reduction has been a consistent finding in various studies of modest size which also connected the inter link structure in basal ganglia and thalamus, other consistent finding in the hippocampus is the reduced GABA function and unusual measure of synaptic density or neuronal plasticity. Further failure of brain derived neurotrophic factor (BDNF) associated neurogenesis or loss of synaptic plasticity is also a causative factor for depression. There is a rise in hippocampal BDNF and camp responsive element binding protein (CREB) mRNA levels in depressive episode patients with prolonged administration of anti depressants, which are found to be low in cerebral cortex of patients with depressive disorders(19).

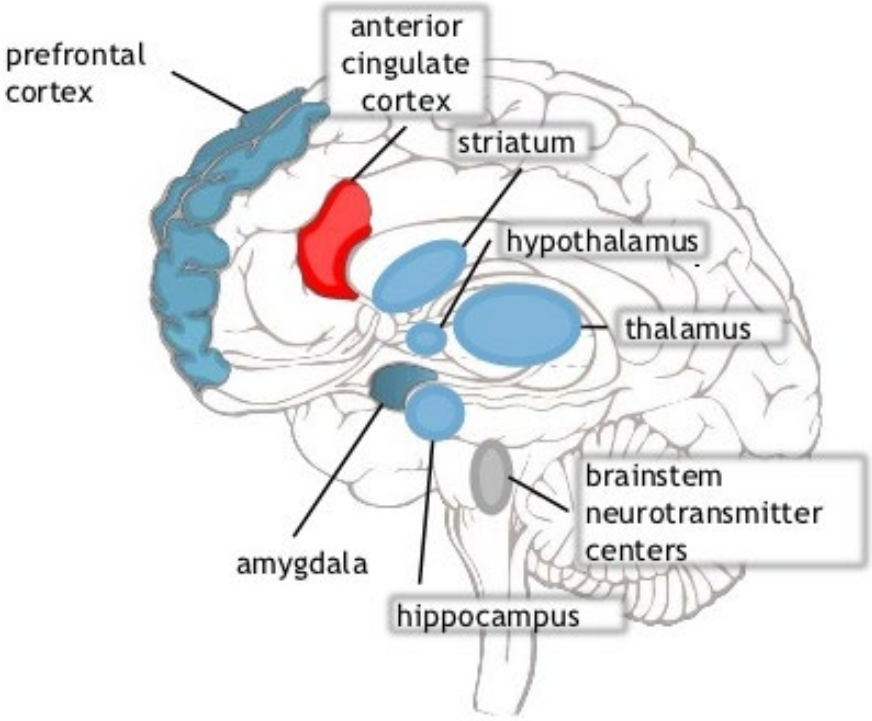

Figure 2: Neuro Anatomy Of Major Depression – Red Areas Shows Hyperactive Areas In Depression And Blue Areas Show Hypoactive Areas In Depression

Currently, all these studies provided treatment options for both pharmacological and non pharmacological approach. A clinical trial explored the Non pharmacological mode of treatment which includes Deep brain stimulation (DBS) by placing electrodes in subgenual cingulated white matter (cg25wm) showed 50% improvement among MDD patients. Other targets for the treatment are lateral habenula, ventral capsule/ventral striatum, and the subcallosal cingulated. Electro convulsive therapy(ECT) ,vagal nerve stimulation and transcranial magnetic stimulation of pre frontal cortex are alternative modes of treating depression(20).

PATHOPHYSIOLOGICAL ASPECTS OF DEPRESSION:

The understanding of pathophysiology of major depression has been a major shift in last decade. The mono amine hypothesis that states that the deficiency in amount and function of monoamines is central to the biology of depression. There is also evidence that involvement of neurotrophic and endocrine factors also play a major role in the pathogenesis of depression.

MONOAMINE HYPOTHESIS AND OTHER NEUROTRANSMITTERS IN DEPRESSION

Mono amine hypothesis suggests that Depression is associated with deficiency of function of cortical and limbic serotonin, norepinephrine and dopamine(21).

Tryptophan depletion

The 5HT1A receptors appear to be decreased in unipolar depression, effect also present in patients who have recovered. The most satisfying evidence that 5HT closely related to mood disorder has come from depletion of tryptophan, the amino acid precursor of 5HT.When the diet is loaded with low protein diet and large neutral amino acids. The levels of tryptophan are increased in both blood and brain which in turn results in reduction of synthesis and release of 5HT. Thus, tryptophan depletion causes clear cut return of severe symptoms with patients who had recovered from major depression while taking a serotonin-selective reuptake inhibitor.

Further, Patients with depressive disorders show serotonergic neurotransmission in serotonergic raphe neurons dysregulation in various areas of brain and disturbance subsequently in cognitive and various physiologic process. Serotonergic receptors such as 5-HT 1A, 5-HT 2A, 5-HT 1B and 5-HT 2C found in the areas of the brain are associated with depression. The increased prevalence of depression in elderly may be due to reduced affinity and density of serotonergic receptors in hippocampal, occipital and cortical areas as the age advances.The action of antidepressants is by directly or indirectly increasing the 5HT interaction with its receptors and preventing the action of respective 5HT transportors. Hydroxyindoleacetic acid (5HIAA) which is metabolic end product of serotonine found to be high in patients with depressive illness whereas reduced in patients responding to the antidepressants(22).

Dopamine

Increase in the binding of D2/3 in the striatum probably reflects a reduced dopamine function either due to a release or secondary upregulation of receptors in patients with depressive disorders.

Hypercortisolaemia

Around half of all patients with major depression have increased cortisol output , which tends to decrease and return to normal on recovery. There is a persistent idea that there is a link between chronic cortisol levels and mood disorders. There is adrenal hypertrophy in major depression measurable in MRI

scan and enhanced response to corticotrophin. This change as in hypercholesterolemia itself reverses on recovery which can be visualized in MRI. A HPA axis programmed to hypersecrete during stressful situations could be a pathogenic mechanism why depression occurs. Major depression is characterized by blunted ACTH response to CRH. Also there is an elevated CRH in cerebrospinal fluid. There is also a postmortem finding which shows increased number of neurons expressing CRH mRNA in paraventricular nucleus of the hypothalamus in patients with depressive disorders (22).

Glial cells

Various number studies suggest the particular involvement of glial cells. The energy requirement of the glial cells is supported by Glial cells. Their deficiency could account for the abnormalities found in this disorder. The increased levels of glucocorticoids acting on glial cells could change their function or primary neuronal withdrawal could represent the changes in the glial cells(22).

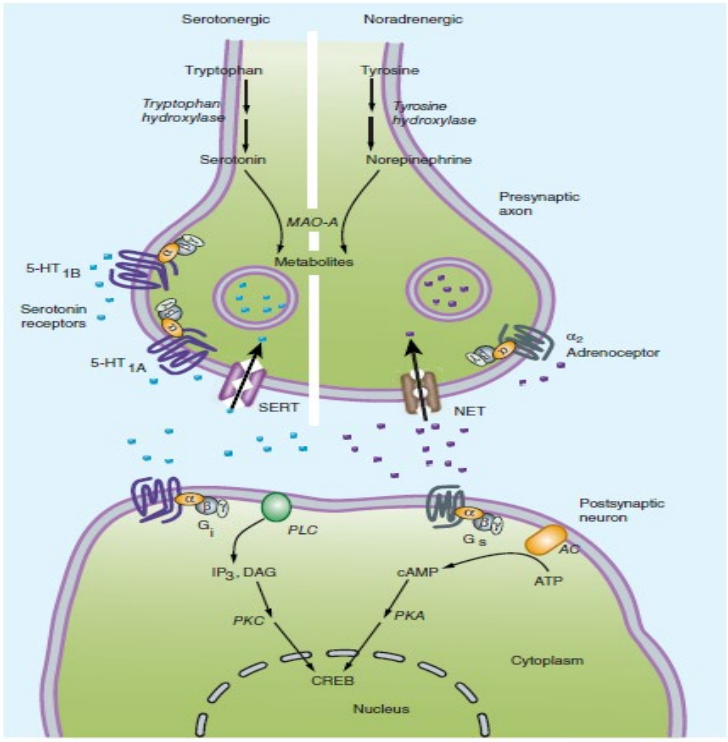

Figure 3: The AMINE HYPOTHESIS of major Depression. Depression appears to be associated with changes in the serotonin and norepinephrine signaling pathway.

NEUROTROPHIC HYPOTHESIS

Research shows strong evidence that the nerve growth factor such as Brain derived neurotrophic factor (BDNF) are important in the regulation of neuroplasticity,resilience and neurogenesis. There is evidence that suggests that depression is linked with the loss of neurotrophic support and the therapies that increase neurogenesis and synaptic connectivity in hippocampus are effective.BDNF has influence on neuronal survival and activates the tyrosine kinase receptor B (tknB) which has growth effects in both neurons and glia (21).

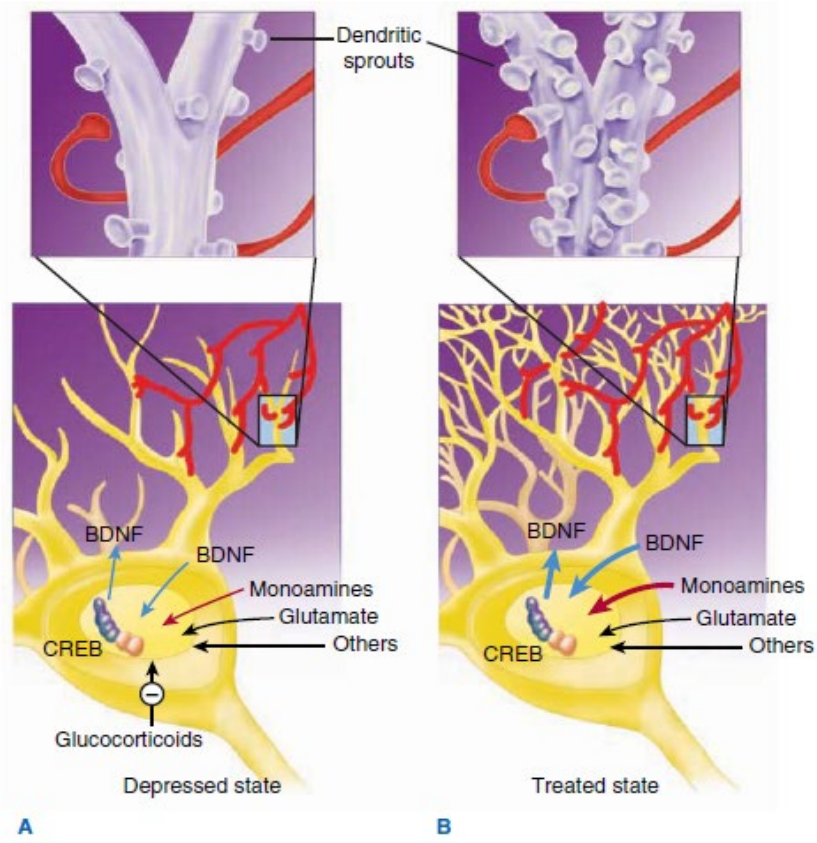

Figure 4: The Neurotrophic Hypothesis Of Major Depression - Changes in trophic factors.

Animal and human studies indicate that the pain and stress are associated with decrease in BDNF levels and loss of neurotrophic support contributes to atrophic changes in hippocampus and medial frontal cortex and anterior cingulate. The direct effects of BDNF on emotional regulation in various researches , when BDNF was given as direct infusion into midbrain,hippocampus, and lateral ventricles of rodents exhibited antidepressant like effect in animal models of depression. Moreover, all antidepressants have shown to increase BDNF levels in animal models with chronic administration. The increase in BDNF levels is associated with increased hippocampal neurogenesis in these animal models. Electro

convulsive therapy used for treating major depression robustly stimulate BDNF levels and hippocampal neurogenesis in animal models of depression. The evidence from the human studies also support the results from animal studies on neurotrophic factor.

A study on cerebrospinal fluid analysis of depressed patients showed decrease in BDNF levels and tyrosine kinase receptor B activity. On the contrary, the treatment with antidepressants showed increase in the BDNF levels in clinical trials which may also be associated with increase in the hippocampus volume. Thus, this hypothesis has been intensely investigated for pathophysiology of depression which yielded new insights and potential targets for the treatment of major depression(21).

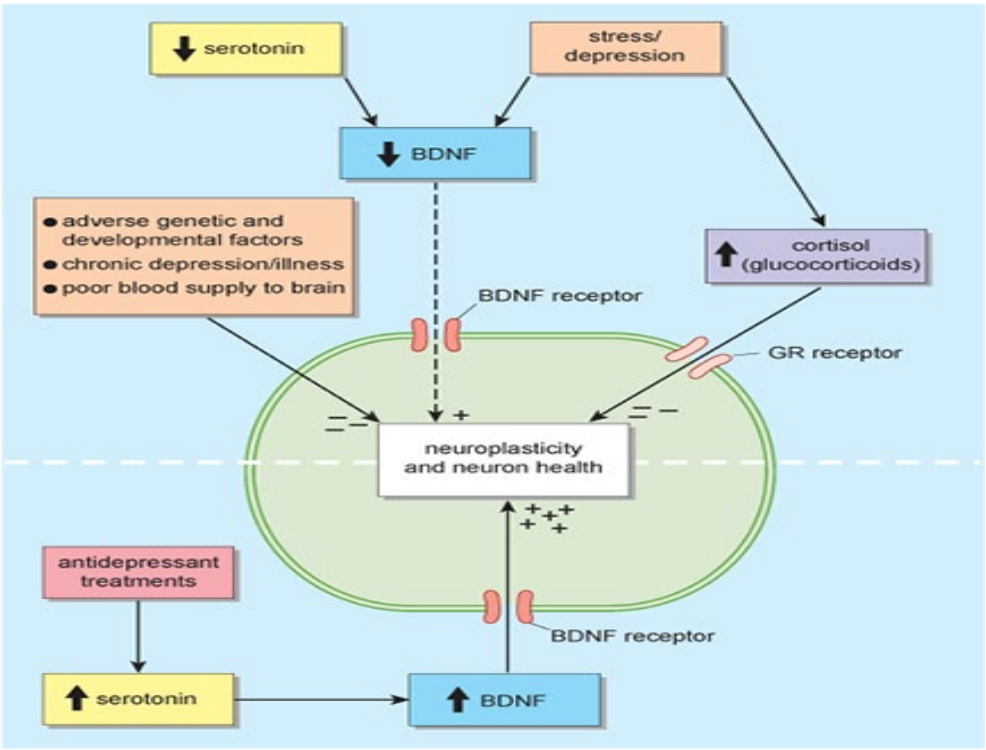

Figure 5: Role of BDNF In Pathophysiology in Depression

RISK FACTORS AND ETIOLOGY OF DEPRESSION:

Many socio demographic variables influence the incidence of depressive disorders. Depression is more prevalent in high risk population as in females, younger age group, poor nutrition, low socio economic status, unemployed, widowers, divorcees, nuclear families in urban areas.Patients with history of stressful life event, chronic health issues, family history of depression, post partum depression, substance abuse are more prone for the illness(22).

AGE

Adolescence by itself is found to be the main attributing factor for depression in this age group. Older adolescents of 8.3% and 20 % of younger adolescents showed clinical signs of depression in a study done in western population. Depression in these age groups often misdiagnosed to be attention disorders. Ultimately all these factors have led to increase in teen suicidal rates, which have increased three times in past 50 years. Subclinical depression as teen will predispose up to 2 to 3 times to major depressive disorder in adulthood. Age of onset of symptoms also plays a significant role in the aspect that earlier onset of disease will become chronic with relapse and recurrence rate at higher range. Thereby, effective diagnosis and treatment will prevent incidence and complications in adult population (9).

The most common psychiatric illness in elderly aged 60 and above is found to be depressive illness in a study done among geriatric population(12). Financial Aspects and health issues are detrimental while good social and family support is helps in reducing the incidence in elderly age groups.

Numerous studies have compared the incidence of depression in various age groups which found that it is more prevalent in late part of life(22).

GENDER

Depression is more prevalent among females with 5.1% and males with 3.6%(7). Global burden of disease report revealed the point prevalence of unipolar depression in men is 1.9% and women is 3.2%, whereas one year prevalence in men and women is estimated to be 5.8% and 9.5% respectively. Ultimately we can conclude that women are at more risk of depression than men. Among women population prevalence during child bearing age group is very high with 20% risk. And the lifetime risk of developing depression varies from 10 -25%(22).

GENETIC INFLUENCE

Depressive disorders and suicide runs in families but the contribution is whether nature or nature is still unclear. However first degree relatives in turn have greater shared risk than half siblings, grandparents or cousins. The risk of depression and stressful life events have been associated with genes that code for the promoter region of serotonin transporter (5HTT) by numerous researchers. Depression that occur at early age are more heritable whereas late onset depressive illness (above) have lowest risk of heritability which is mostly associated with the acquired risk factor such as cerebrovascular disease(22).

CHILDHOOD EXPERIENCES

Studies examined the nature of child parent attachment and found that that lack of parental care was consistently associated with increased rates of depression. Recent research shows, childhood sexual abuse has been established as a risk factor for major depression in adulthood. Cumulative childhood disadvantage certainly pose a greater risk of depression than a

isolated event. On contrary, childhood resilience, one good relationship with adult and intelligence in child may protect from other adversities(19).

PERSONALITY

Long history of interest has been seen linking personality traits and vulnerability to depression. Likely individuals exhibit undulyanxiety,impulsiveness and obsession show greater risk of major depression. Neuroticism has been seen as a risk factor , same genes may be associated with initial development of neuroticism and later to anxiety and depression(19).

SOCIAL ENVIRONMENT

Interest in the role of marital status has been a risk factor for depression. For men, the divorced men have higher rate of depression than married man who show lower rate of depression. The stressors associated with separation or divorce could increase the occurrence of depression. Adverse life events are a well established risk factor. Increased vulnerability to the illness is more during first few months after such events. Genetic influence of an individual also increase the sensitivity to such life events and finally predisposing to the illness(22).

SOCIAL STRESSORS

Chronic stressors play a more important role than acute stressors in the development of major mood disorders.(eg.difficult marriage or

unemployment). The accumulation of negative stressful events is the strongest predisposing factor. The different nature of social stressors in individual living in urban community may be the major source for their higher psychiatric morbidity(23).

SOCIAL SUPPORT

The lack of social support including social interaction and social network can be a major risk factor. Regarding the social interaction the frequency plays a major role than amount of interaction (23).

SOCIO-ECONOMIC STATUS AND DEPRESSION

Comparatively Lower socio economic status people show higher prevalence of depression. The prevalence rises with decreasing social economic status(22).

MATERNAL HEALTH AND DEPRESSION:

Depression diagnosed during antenatal period may have poor self care, engage in alcohol and drug abuse which is harmful for the fetus. All these factors produce decreased or abnormal development in fetus, which in turn increases the risk of pre-eclampsia, leading to low birth weight, malnourishment and chronically ill infants.

Depression in perinatal period also affects social, language and cognitive development of the off spring. Even after adjusting the confounding factors of social economic status and the factors, depression in perinatal period in mothers have 5 times higher risk of infants with poor nutrition and growth delay which is evident from 6 months of age. There is a 5 times more risk of

developing depression in children with depressed moms when compared to non depressed mothers .(22) Depression is significantly higher during perinatal period and incidence of post partum depression is 11%(23).

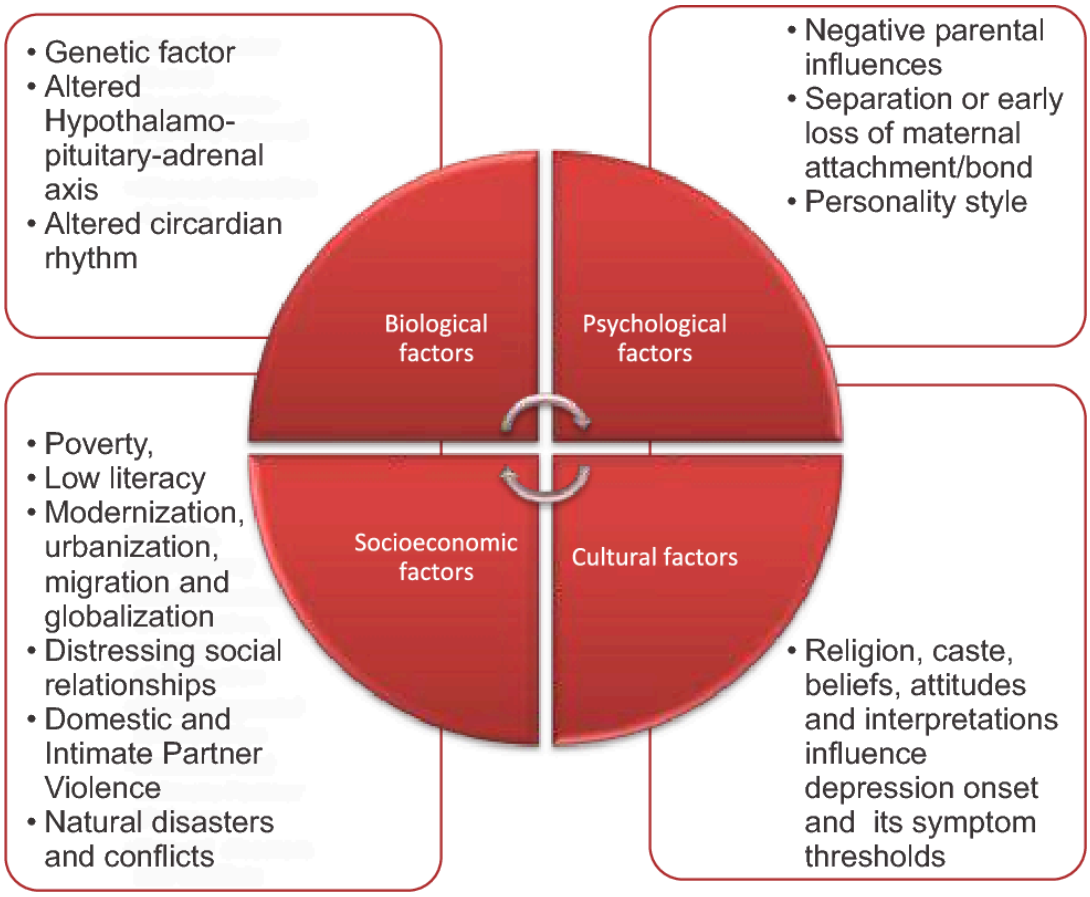

Figure 6: Risk Factors and Etiology of Depression

On conclusion , the epidemiological for the prevalence of depressive illness shows higher incidence among females, geriatric population, positive family history, low socio economic status, poor nutritional status, also among

individuals who are unemployed, single, divorced or widowed and those living in urban areas and nuclear families(22).

DISEASES COMMONLY ASSOCIATED WITH DEPRESSION

Depression is often associated with other systemic illness like malignancy, diabetes mellitus, epilepsy, post stroke, multiple sclerosis. It is most commonly associated with certain endocrine illness like cushing's disease, hypothyroidism. Neurological disorders like parkinsonism, alzheimers disease, huntington's disease, wilsons disease, cns tumors, infarcts, injury to frontal lobe, striatum and medial mesotemporal cortex predispose to depressive illness. Out of all the neurological illness parkinsonism has four times higher risk of developing depressive illness(24).

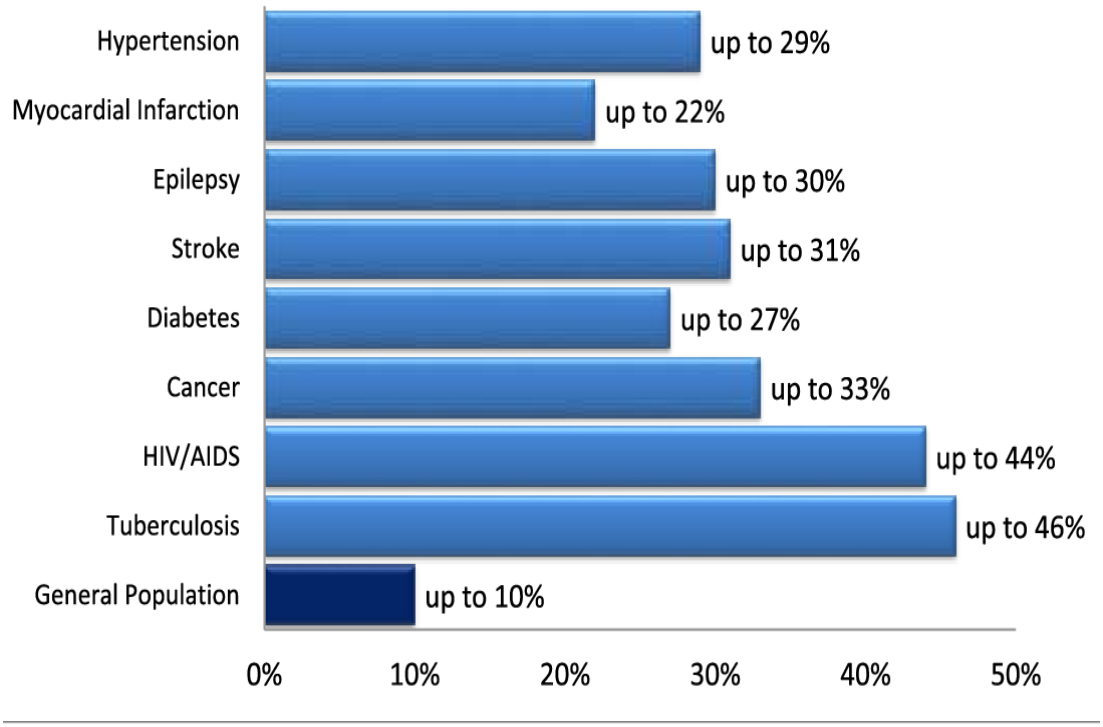

Figure 7: Prevalence Of Illness Associated WithDepression- WHO report 2003

DRUGS CAUSING DEPRESSION

- Chemotherapeutic agents like asparaginase, azathioprine, vincristine, vinblastine and bleomycin in addition have a direct role in causing depression.
- Cardiovascular drugs like ACE inhibitors, calcium channel blockers, digitalis and clonidine are also found to precipitate depression in susceptible individuals. Statins widely prescribed in most of atherosclerotic or degenerative disorders has found to have a role in development of depression in susceptible individuals.

- Anti hypertensive drug, methyldopa often used for treating PIH in pregnant women is also implicated in causing depression.
- Other drugs that can increase the risk of depression are anti-parkinsonian drugs like amantadine, levodopa and bromocriptine. Anti-psychotics like haloperidol, anti epileptics like phenytoin, ethosuximide, tiagabine, vigabatrin.
- Anti microbials like ampicillin, chloroquine, dapsone, anti-tubercular drugs like isoniazid, ethambutol. Anti retroviral drugs like atazanavir, efavirenz,saquinavir, zidovudine also can cause depression.
- NSAIDS, antihistaminics like ranitidine, and cholinergic drug physostigmine are predispose to depression(25).
- Hormonal agents like oral contraceptive pills and tamoxifen can cause depression. Prednisolone and Reserpine simulate endocrine and neurochemical changes similar to the changes observed in endogenous Major Depressive Disorder. Prednisolone causes hypercortisolism, while reserpine deplete mono amine transmitters which in turn precipitates a Major Depressive Episode in vulnerable population (24).

DEPRESSION INDUCED CO-MORBIDITIES

Co-morbidity can be explained as the presence of one disorder or disease in a patient, increasing the risk or prevalence of another disease in the same patient. This simultaneous occurrence of two diseases together can affect the course of both diseases(26). In patients with major depressive disorder,

several medical conditions show higher risk of occurrence, of which increased prevalence of coronary events and stroke in depression are proven by number of studies. Risk of developing stroke in patients with depression or with a history of depressive illness is found to be two to three times higher than among those without depression. This risk prediction is obtained after ruling out the influence of confounding factors of diabetes, hypertension, tobacco use(27).

According to a quantitative review, depression is a proven independent risk factor that can contribute for a significant increase in the incidence of coronary heart disease. This risk is greater than passive smoking for the development of coronary events(28). Apart from the higher risk of occurrence of these co-morbidities, depression is also found to increase the risk of death, especially more by cardiovascular diseases and unnatural causes(29).

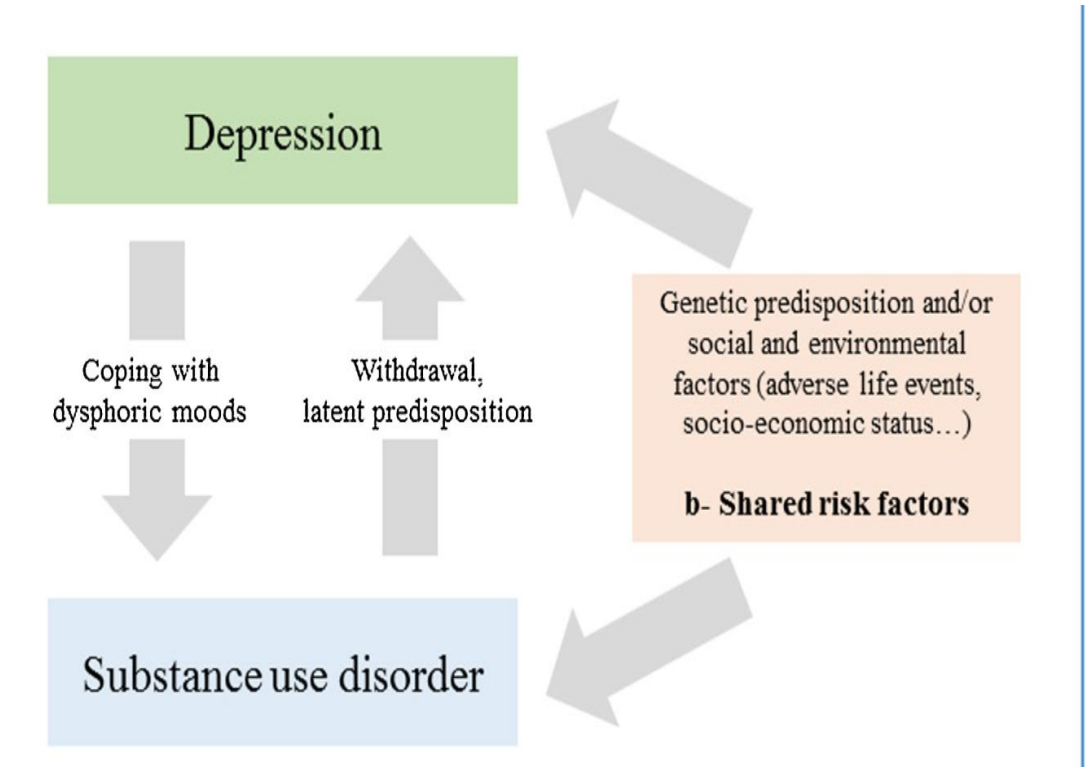

Figure 8:Relationship between Depression and Substance use disorder

SYMPTOMS

DSM (Diagnostic and Statistical Manual of Mental Disorders) is the manual with international standards which documents about mental disorders by expert in mental health and associated professional fields for dealing with mental disorders. American psychiatrist Dr. Jeffrey Liebermann and Dr. Thomas Insel credit DSM as the best information brochure along with ICD, presently providing all necessary details for the clinical diagnosis of mental disorders(30).

According to DSM V, major depressive disorder is characterized by the following symptoms namely,

Table 1: Symptoms of Major Depressive Disorder – DSM V

SI.No.	SYMPTOMS
1.	Depressed mood
2.	Markedly diminished interest or pleasure
3.	Feelings of worthlessness or inappropriate guilt
4.	Insomnia or hypersomnia
5.	Psychomotor agitation or retardation
6.	Fatigue or loss of energy
7.	Increase or decrease in either weight or appetite
8.	Diminished ability to think or concentrate, or indecisiveness
9.	Recurrent thoughts of death or recurrent suicidal ideation

To declare a patient to be depressed he or she must have any 5 of the above symptoms inclusive of anhedonia or depressed mood.

Depressed Mood

This term refers to a negative affective arousal described in many ways as depressed,mournful,irritable or anxious. The depressed mood is typically experienced as worse than a severest physical pain, usually in the severe form. In moderately depressed mood exhibits in a form of groundless apprehensions with severe inner turmoil and torment which is typically seen in elderly and adult persons. Suicide may seem as a solution to this inner torment and death may be conceived comforting. In elderly patients, physicians should suspect the

presence of mood disorders by patient's facial expression, vocal inflection, and overall appearance(31) .

Anhedonia and Loss of interest.

There is a paradoxically heightened perception of pain in many persons with depression accompanied by inability to experience normal emotions. Patients loose their sense of pleasure in previously enjoyable activities termed as anhedonia. Mild patients present with decreased interest in life but in severe form patients complain as loss of interest in all things in life and also complain of depersonalization, being cut off from their life and derealization. Anhedonic patients may be so severe that the person may loose beliefs and values that had major meaning in their life. Patients ultimately suffer from inability to experience emotions(31).

Psychomotor Activity

In younger patients (< 40 year old), retardation is more common and is characterized by slowed thinking and Activity, decreased energy and monotonous voice. In a severe form, the patient can become stuporus (depressive stupor). In the older patients (e.g. Post-menopausal women), agitation is commoner. It often presents with marked anxiety, restlessness and a subjective feeling of unease. Irritability may present as easy annoyance and frustration in day-to-day activities(23)**.**

Physical Symptoms

Various physical symptoms (such as heaviness of head, vague body aches) are particularly common in the elderly depressives and depressed patients from the developing countries like India. These physical symptoms are almost always present in severe depressive episode. Another common symptom is the complaints of reduced energy and easy fatigability (12).

Biological Functions

Disturbance of biological functions is common, with insomnia /hypersomnia, loss of appetite and weight/ hyperphagia and weight gain, and loss of sexual drive. The presence of somatic syndrome in depressive disorder signifies higher severity and more biological nature of the disturbance (12).

Suicide

Suicidal ideas in depression should always be taken very seriously. Although there is a risk of suicide in every depressed patient with suicidal ideation, presence of certain factors increases the risk of suicide. (12) One major and severe complication of depression is suicide. According to estimates of Indian Union Health ministry, there are about 120,000 suicides reported every year. Out of ten individuals who die by suicide, nine of them have been found to be affected by psychiatric illness, of which depression is implicated as the most common cause. Among patients who die while on treatment for depression, 1 out of 6 deaths is due to suicide(32).

Absence of Underlying Organic Cause

If depressive episode is secondary to an organic cause, a diagnosis of organicmood disordershould be made. In ICD-10, the severity of depressive episode is defined as mild, moderate or severe, depending primarily on the number of the symptoms, but also on the severity of symptoms and the degree of impairment (12).

SCALES FOR ASSESSMENT OF SEVERITY OF DEPRESSION

Various standard recommended scales that are available currently forassessment of severity of depression is shown in the table below:

Table 2: Types of Scales for Assessment of Severity of Depression

SI.No.	Scales for Assessment of Severity of Depression
1.	MADRS (Montgomery-Asberg Depression Rating Scale)
2.	HAM-D (Hamilton Depression rating scale)(HAM-D17, HAMD21,HAM-D24)
3.	CGI scale (Clinical Global Impression)
4.	QIDS (The 16-item Quick Inventory of Depressive Symptomatology)
5.	IDS (The 30-item Inventory of Depressive Symptomatology)

Currently available guidelines for treating depressive illness lay emphasis on the assessment of severity of symptoms and disease before deciding upon patient's initial therapy. The Montogomery–Asberg depression rating scale(MADRS) is widely used in depression measures in research and clinical setting(33). The MADRS has been found have strong psychometric

properties among patients with depressive disorders and have shown to discriminate between grades of depression(34,35).

It was specifically developed to assess sensitive changes in depressive symptoms over time making it a useful tool for monitoring treating patients**(36)**. Studies found the MADRS to have a high sensitivity and specificity compared to a clinical diagnosis of a depressive disorder. In a study that compared HAM-D and MADRS, MADRS appeared to be more sensitive than the Hamilton scale(37) .

Each MADRS item yields a score of 0 to 6 and the MADRS test with ten variables ranges from 0 to 60 and was rated as follows(38):

Table 3: Assessment of Severity of Depression using MADRS Score

MADRS score	ASSESSMENT
0-6	NO DEPRESSION
7-19	MILD DEPRESSION
20-34	MODERATE DEPRESSION
35-60	SEVERE DEPRESSION

Currently available guidelines for treating depression, lays emphasis on the assessment of severity of symptoms anddisease before deciding upon patient's initial therapy. Apart from these scoring, severity can be labeled based

on the need for hospitalization, depressive subtypes and functional capacity of the patient. The assessment of the therapeutic response may be done using various scales mentioned above and the use of the same parameters yield better assessment of the treatment given and it can be applied at different time intervals for the same patients.

MANAGEMENT OF DEPRESSION

Pharmacotherapy is the first choice in severe depression in depressive disorders as per guidelines, while psychotherapy is more limited to acute phase of the illness. In patients with mild to moderate depression both pharmacotherapy and psychotherapy are recommended options(34).

PSYCHOTHERAPY FOR DEPRESSION

The psychotherapeutic interventions include

1.**Behavioural therapy** deals with social skills, training and problem solving.

2. **Cognitive behavioral therapy (CBT**) majorly features by identifying problems, cognitive distortions/errors, alternative though generation, problem solving and management strategies along with relaxation exercises.

3. **Interpersonal therapy** deals with role disputes and transitions, social skill deficits and other interpersonal factors which play a role in development of depression.

4. **Supportive psychotherapy** enables patient to communicate and provides emotional support. It helps to increase patient's self□esteem, enhancing hope, enhancing adaptive coping.

5. **Marital Therapy (MT)** is the treatment which includes behavioral exchange, communication training, problem solving, and resolution of conflict between both members involved in marital relationship.

6. **Family Therapy**- it involves all the members in the family when family dynamics are responsible for depression.

7. **Brief Psychodynamic Psychotherapy (BPD)** involves training the individual to learn methods to cope with inner conflicts(25).

The **PHYSICAL THERAPY**includes,

1.**Electroconvulsive therapy (ECT)**

It is one of the earliest of modern treatments, yet most effective in severe depression. It has been found more effective than simulated ECT in blind trials as well as pharmacotherapy as given by a meta-analysis (12). Unilateral appears to be less effective than bilateral ECT. Psychotic depression with delusions or psychomotor retardation show best improvement with this treatment.

2. OTHER PHYSICAL TREATMENTS

(a) Bright light

This may be an established treatment for seasonal depression. However many studies have showed improvement in nonseasonal disorders too. But the effect may not be sustained (22).

TREATMENT GUIDE

Treatment guide for depression in different grades of depression are as follows,

- **Acute phase treatments** are given for 6-12 weeks mainly aimed for achieving remission. The acute phase treatment should include comprehensive medical, psychiatric and psychosocial assessment ensuring the patient safety. Based on the patient appropriate treatment modality of psychotherapy, pharmacotherapy or both is chosen, also adjuvantmedications or electro convulsive therapy is considered depending upon the patient's clinical assessment.

Mild and moderate depression is treated with either one of the entity whereas severe form may be treated with combination of treatment modality. However the basic steps for evaluation of the type, severity, social stressors past history, response to previous treatment, family history ,psychiatric co morbidities are all common for both(25).

In mild to moderate depression, where there is no past history with good response to psycho and pharmacotherapy or psycho social stressor that can be altered or high drug interaction risk psychotherapy is preferred. If the clinical improvement is not seen with psychotherapy then those patients can be treated with anti depressants.

In moderate depression, if there is good response to treatment in past and when there is a low risk of drug interactions pharmacotherapy is the preferred modality of treatment. If the patient doesn't respond to one anti depressant, change or adding of other anti depressants has to be considered.

Patients with partial response have to be treated with more aggressive psychotherapy and maximum tolerable dose of antidepressants can be done for optimized treatment. Safety and tolerability has to be considered during augmentation of any anti depressants.

In severe depression, pharmacotherapy is preferred modality for those with good response to the therapy in past episodes. Electroconvulsive therapy has to be considered for acute phase, management of severely depressed patients with suicidal thoughts, poor oral intake, catatonic symptoms and poor response to pharmacotherapy.

- **Continuation phase treatment** aims at maintaining the optimum response achieved in acute phase and prevent relapse. It's for period of 16-24 weeks. The patients who are treated with anti depressants same dose has to be continued for 6-9 months after achieving remission. For patients treated with psychotherapy alone the same or reduced frequency for 6-9 months after achieving remission. In patients with combination of treatment same anti depressants and same frequency of psychotherapy is advised for 6-9 months.

- **Maintenance phase** of treatment for continuing anti depressants for prolonged duration is recommended for patients with past history of depression. The maintenance treatment duration is individualized based on their response, past episodes and relapse rates. The same anti

depressants and same dose is recommended in maintenance phase, whereas frequency of visits for cognitive behavioral therapy and interpersonal therapy can be reduced.

- **Treatment discontinuation** is considered in patient with no past history of the disease and patient who are clinically stable after continuation phase. The discontinuation is done in form of tapering the dose from weeks to months so as to avoid discontinuation syndrome. This tapering over a period of time enables to asses for recurrence ofsymptoms. Psychotherapy discontinuation is dependent on the patients needs. All patients should be monitored for relapses after discontinuation of treatment.

MANAGEMENT OF DEPRESSION ASSOCIATED WITH OTHER SYSTEMIC DISEASES:

Bronchial asthma patients should not be treated with MAOs as they interact with sympathomimetic bronchodilators during the course of treatment.The SSRISs, bupropion, newer anti depressants and ECT are safer options for patients suffering from cardiac diseases like ventricular arrhythmia, subclinical sinus node dysfunction, conduction defects, or recent MI. Use of tricyclic antidepressants should be avoided.

Patients suffering from glaucoma may be treated with antidepressants without anti cholinergic activity like bupropion,SSRIs and trazadone.

TCA interact with antihypertensive by either intensifying or counteract the effect of antihypertensive therapy their antagonist the therapeutic actions of various antihypertensives like guanethidine, clonidine and alpha methyldopa. Concurrent therapy with trazadone or maoisMAOs will induce symptomatic orthostatic hypotension. Venlafaxine causes dose dependant increase in blood pressure so less favorable in hypertensives(39).

PHARMACOTHERAPY FOR DEPRESSION

Anti depressant drugs available till date can be classified as follows.

1. **MAO inhibitors**

   Non-Selective; Tranylcypromine

   Selective MAO-A inhibitor: Moclobemide

2. **Drugs which block NE and 5-HT reuptake**

Tricyclic Antidepressants (TCAs): Imipramine, Clomipramine, Amitriptyline, Doxepin

3. **Drugs that mainly block NE reuptake(NRI)**

   Desipramine, Nortriptyline, Protriptyline, Maprotiline, Amoxapine, Reboxetine.

4. **Serotonin-Norepinephrine reuptake inhibitors (SNRIS)**

   Duloxetine, Venlafaxine, Desvenlafaxine, Milnacipran, Levomilnacipra

5. **Selective Serotonin Reuptake Inhibitors (SSRI)**

Sertraline, Fluoxetine, Fluoxamine, Paroxetine, vortioxetine, Citalopram, Escitalopram

ATYPICAL ANTI-DEPRESSANTS

- **5-HT receptor modulators** :Trazodone, Nefazodone, Vortioxetine
- **Tetracyclic &Unicyclic agents:** Bupropion, Mianserin.
- **Norepinephrine Serotonin Reuptake Enhancer (NSRE)** - Tianeptine.
- **Noradrenaline And Specific Serotonin Antidepressant (NASSA)**– Mirtazepine
- **Serotonin partial agonist reuptake inhibitor (SPARI)**–Vilazodone
- **Anti depressant of natural origin** - St. John's wort(25,40).

General features of ANTI-DEPRESSANTS

The chief sites of action are noradrenergic nerve terminal and serotonergic nerve terminal. Drugs such as SSRIs, SNRIs and TCA inhibit the norepinephrine transporter or serotonergic transporter (NET or SERT) which in turn increases noradrenergic or serotonergic neurotransmission contributing to anti depressant effect.

Mono amine oxidase (MAO) is an enzyme responsible for metabolizing serotonin and norepinephrine. The drugs that inhibit MAO, inhibits the catabolism leading to increase in the concentration of norepinephrine and serotonin at the synapse.

Atypical anti depressants namely Trazadone acts directly on serotonergic receptors(41).Common encounter with all the anti depressants is that the biological lag for about 2 to 3 weeks for the clinically evident antidepressant effect. Although monoamine reuptake is instant, complete therapeutic effect is evident only after the down regulation of post synaptic beta1 beta2, 5HT receptors accompanied with desensitization of pre synaptic alpha 2 and 5HT1 Autoreceptors(21). Long term treatment with many anti depressants produces desensitization of presynaptic auto receptors and heteroreceptors which produces persistent changes in mono aminergic neurotransmission. These effects are mediated by their post captor modulation which includes GPCR modulation protein kinase and ion channel activation(41).

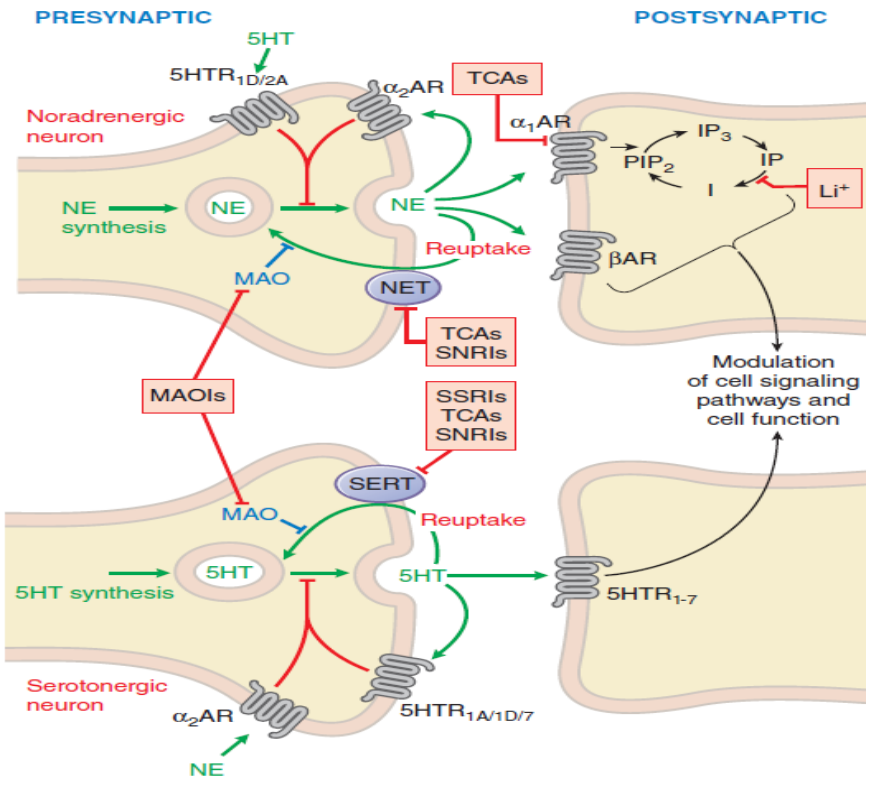

Figure 9: Sites Of Antidepressant Drugs Action

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

Many drugs were introduced since 1984 under the group of SSRIs which includes fluvoxamine, fluoxetine, paroxetine, sertraline, citalopram, escitalopram. The drugs have been used for obsessive compulsive disorder, generalized anxiety, pre menstrualdysphoric disorder also other off label use of many psychiatric, medical and behavioral conditions. All the SSRIs have proven to have good safety profile and few well known for their efficacy in managing the major depression patients. Numerous studies demonstrated the there is at least 50% remission in about 6-8 weeks of treatment. It also improves cognition and motor functional capacity due to its neuronal plasticity(42).

MECHANISM OF ACTION

As the name suggests, it inhibits the serotonin transporter mediated reuptake of the serotonin at the synaptic cleft and in some somato-dendritic area, increasing the serotonin concentration along with the down regulation of auto-receptors which causes increases concentration of serotonin at the synaptic cleft(40). They bind at a different site of the serotonin transporter. Initial treatment with SSRIs causes auto receptor stimulation which leads to reduction in synthesis and release of serotonin. Gradually, it causes downregulation and auto receptor desensitization of the auto receptors producing anti depressant effect.

Also it causes downregulation of post synaptic 5HT2A receptors also contributes to the anti depressant effect either directly or by influencing the Noradrenergic function through serotonergic hetero receptors. At higher concentration of serotonin at 5HT receptors synaptic cleft produces therapeutic effect of SSRIs(19).

Late effects are also essential for producing a sustained therapeutic effect. They are mediated by constant rise in the cyclin AMP singnaling leading to CREB (cAMP response element binding protein) nuclear transcription factor phosphorylation, increased expression of BDNF,its receptor trkb and other trophic factors.

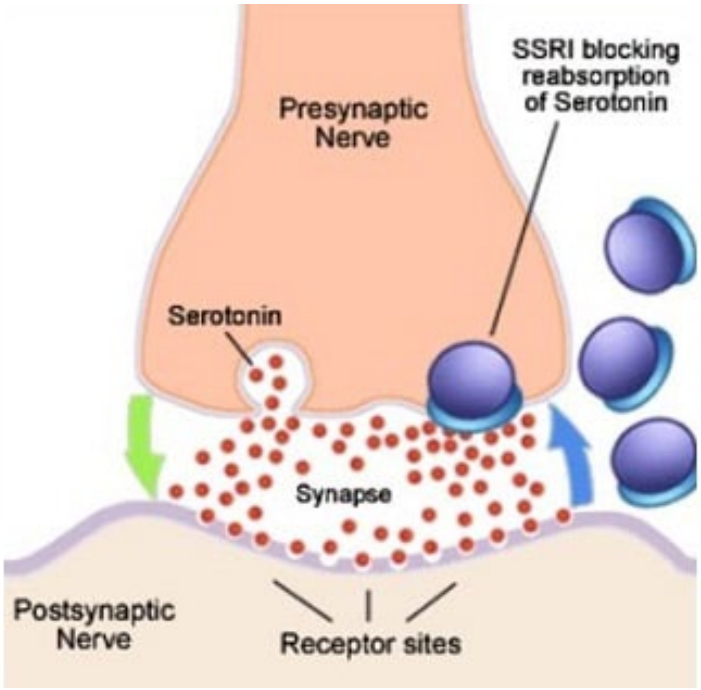

Figure 10:Mechanism Of Action Of SSRIs

Furthermore, there is increased neurogenesis from the progenitor cells in the regions of dentate nucleus of hippocampus and sub ventricular zone during the treatment with SSRIs. In the animal models of depression while on SSRIs, increased neurogenesis dependant behavioral effects were seen. Prolonged treatment also produced reduced expression of SERT (serotonin transporters) which increases the serotonergic transmission by decreasing the synaptic clearance, which was also evident in the animal models on SSRIs(41).

Adverse effects

- Increased serotonergic action on 5HT3 in GIT causes nausea, diarrhea and other associated GI symptoms. It usually occurs in the early phase of the treatment and reduces after 1st week.
- SSRIs increase tone throughout the body including brain and spinal cord due to its serotonergic action.
- Sexual dysfunction is seed in one third of the patients treated with SSRIs. Enhanced serotonergic action on 5HT2 receptors present in the spinal cord causes sexual dysfunction which includes decreased or loss of libido, delayed ejaculation and delayed orgasm or anorgasmia. In animal studies with SSRIs shows that increased serotonin in CNS reduce the dopamine levels which has a role in normal sexual functioning(43).These effects may decrease with time.
- SSRIs usually do not affect weight of the patient except paroxetine which causes weight gain.

- Headaches, insomnia and hypersomnia can occur due to increased serotonin ;levels acting on 5HT2 in brain(21).
- Slow titrated dose is recommended as SSRIs may produce anxiety and agitation in few patients(40)Few studies show that SSRIs are associated with occurrence of drug induced parkinsonism, dystonia, dyskinesia and akathsias(44)Although rare but various case reports, observational studies as well as prospective clinical trial have reported potentially serious adverse drug reaction hyponatremia varies from 0.5% to 32%. The risk factors associated with the development of hyponatremia with SSRIs are elderly, females, concomitant use of diuretics, low baseline sodium concentration. It usually occurs within first few weeks and resolved within 2 weeks of discontinuation(45). The mechanism associated with this ADR is secondary to the development of SIADH(46).As these drugs are firstline to treat depression in elderly , it should be prescribed with caution due to this potential adverse effect
- Discontinuation syndrome is produced with SSRIs with shorter half life. This occurs due to abrupt stoppage of the drug after a chronic use (atleast 6weeks). When these drugs are prescribed on the long time they block the SERT, downregulation of the receptors along with less serotonin and other neurotransmitters in the synaptic cleft producing these syndrome(47). SSRIs with MAO inhibitors have pharmacodynamic drug interaction which produces a serious adverse effect namely Serotonin syndrome(21).

NEW TREATMENT OPTIONS CURRENTLY AVAILABLE

MULTIMODAL ANTI DEPRESSANTS

Multi modal\Multi functional Antidepressants have more than one mode of action. Although these multi modal mechanisms like reuptake inhibition and activity on membrane –bound receptors, pooling two distinct modes of neural signaling effects produce a downstream effect on inter connected neurotransmitters systems, the difference among them are based on their action at receptor subtypes. The efficacy of new multimodal anti depressants has not yet been tested in treatment resistant depression (48). The new antidepressants under this category are voertioxetine and vilazodone have their targets on serotonoin receptors 5-HT1A, 5-HT3, and 5-HT7 have their specific effects on certain symptoms of depression. Drugs that target glutamatergic system open a promising new territory for drug development for the patients with major depression.

KETAMINE

Ketamine is an anesthetic drug with -methyl-d-aspartate (NMDA) glutamate receptor antagonist activity. It may provide a new anti depressant mechanism. According to the systematic search for randomized trials, Ketamine have a rapid but transient anti depressant effect. However, the heterogenecity in clinical response has been substantial. The underlying mechanisms of actions are not completely understood(49,50). The response with single intravenous dose of glutamatergic modulator ketamine produces rapid anti depressant effect that opened the way for other more selective glutamatergic modulators such as intra nasal Esketamine ,Rapastinel(51).

NEW DRUGS

OPIOIDS

The anti depressant potential of opioids has been known for centuries, however the dependence was a major drawback. At recent times the preclinical and clinical evidence supporting the hypothesis that the endogenous opioid system deregulation for mood disorders is emerging. The use of regular opioid agonist as anti depressants in clinical practice is highly limited due to its dependence and abuse. The limitations have been overcome by opioid partial agonist buprenorphine and mu opioid antagonist samidorphan.Multicentric, randomised, double blind ,placebo controlled study have revealed that the modulation of the opiate system may be a novel treatment approach for treatment resistant depression (52).

PSYCHEDELICS

The psychedelic drugs like lysergic acid, psilocybin were used extensively in the treatment of various mood disorders and several other psychiatric conditions before their ban in late 1960s.A recent systematic review of clinical treatment studies using psychedelics in patients with depression showed clinician judged improvement after treatment with psychedelics(53). A recent pilot study in UK favors the use of psilocybin in treatment of treatment resistant depression. Their exert therapeutic effect by acutely destabilizing local brain networks providing resetting after the acute effects have resolved(54).

NEW AUGMENTATION STRATEGY

The evidence based augmentation of certain serotonin uptake inhibitors is an augmentation with atypical anti psychotics. Brexipiprazole, a new partial dopamine agonist enlarged the spectrum of atypical antipsychotics used for depression. Depression is not simply a result of derangement of neurotransmitters.

A large number of evidence points towards deregulated endocrine and inflammatory responses and reduced neurogenesis in MDD pathogenesis. It is also associated with regulation of immune response system with chronic inflammatory activities which are reflected by abnormal profiles of circulating pro and anti inflammatory cytokine.

Numerous studies indicate that the adjuvant use of anti inflammatory agents in patients with major depression improves depressive symptoms particularly in treatment resistant depression with increased inflammatory markers.

This may be more useful in the sub group of patients that have clinical features of trauma ,resistance to anti depressants and raised interleukin-1 levels(55).

Recently, several reviews showed the efficacy of safe augmentation strategy- nutraceuticals. The adjuvant therapy of standardized pharmaceutical grade nutrients referred to as nutraceuticals. Provide a safe and effective

approach by enhancing the anti depressants effect. They act either by synergistically augmenting a particular activity of anti depressants or by providing a whole different range of additional biological effect.

All the nutraceuticals are generally well tolerated, with minimum gastrointestinal side effects. Current evidence support the adjuvants such as S-adenosylmethionine, methylfolate, omega-3, and vitamin D with anti depressants to reduce depressive symptoms(56).

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (TMS)

In a study with left prefrontal TMS showed superiority compared with sham therapy. There is a weak effect also the optimal parameters for stimulation has no sufficient evidence. Thereby widespread use for TMS is not currently practiced.

VAGUS NERVE STIMULATION

In various countries the left afferent left cervical nerve fibres by a stimulator implanted in the chest wall is approved for resistant depression and resistant epilepsy. Sufficient data is not available for routine use(22).

DEEP BRAIN STIMULATION

Chronic stimulation of white matter tracts adjacent to the subgenual cingulate region by implanted electrodes has been reported to produce marked remission in few patients with resistant depression, who are associated with

marked reduction in local cerebral blood Flow(22). However further evidence is needed.

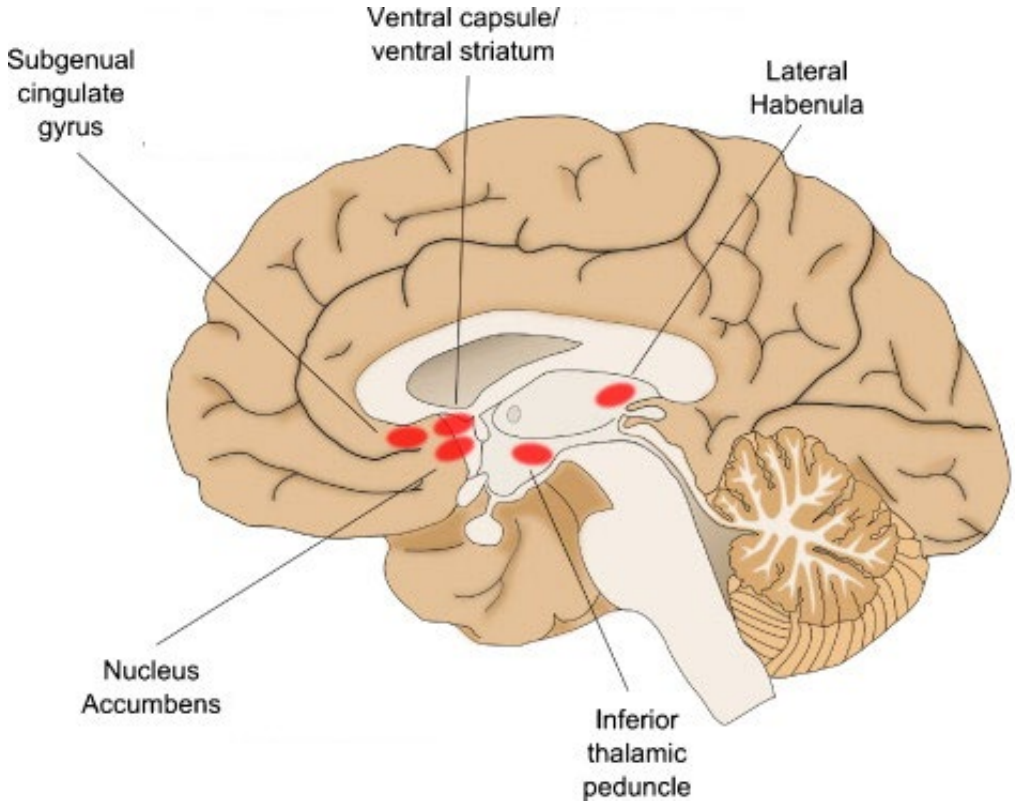

Figure 11:Areas For Deep Brain Stimulation In Treatment - Resistant Depression

ACETYL L CARNITINE

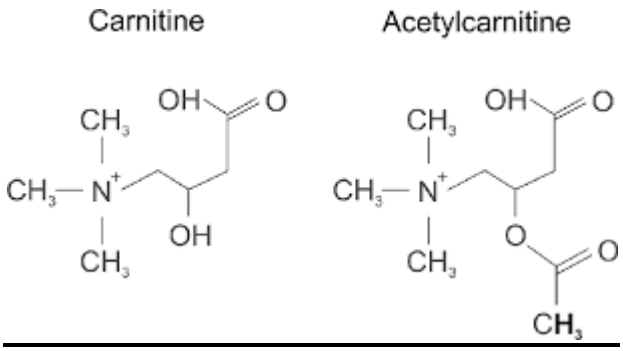

Figure 12: Chemical Structure of Acetyl-L-Carnitine

ALCAR, an endogenous compound, is the short ester of carnitine L isomer that acts as a donor of acetyl groups and facilitates the transfer of fatty acids from cytosol to mitochondria duringB-oxidation(57). The functions of L carnitine includes transport of long chain fatty acids across the mitochondrial membranes into the mitochondria and transport of small chain and medium chain fatty acids out of the mitochondria in order to ,among other things maintain normal co enzymes levels in organelles. The acetyl component provides for the formation of the neurotransmitter acetylcholine.

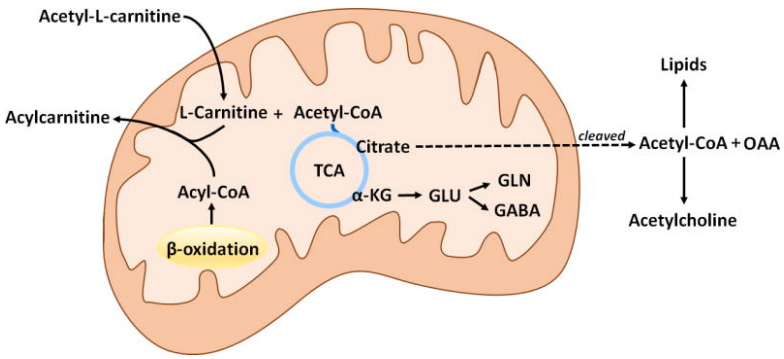

Figure 13: Action of ALCAR in Mitochondria

PHARMACOKINETICS

ALCAR could be administered orally, intravenously, and intramuscularly. They are absorbed in the small intestine via simple diffusion(58). It is transportedInto intra-cellular tissues through active transporters, and plasma concentrations of ALCAR andL-carnitine reached equilibrium via carnitine acetyl-transferase activity. It can also readilyCross the blood-brain barrier mainly via Na+-dependent transporters, and its primaryClearance route is assumed to be renalhalf life of ALCAR is 4.2 hours(59). ALCAR undergo minimal metabolism and are subsequently excreted in the urine via renal tubular reabsorption. The rate of clearance increases with the plasma concentration of these substances.

THERAPEUTIC DOSES

- **Adult IV**: 50 to 300 mg/kg depending upon the indication.
- **Oral**: 1 to 3 grams or 100mg/kg depending upon the indication

Toxicity: intravenous doses as high as 300mg/kg have been administered with no apparent toxicity

MECHANISM OF ACTION

Numerous preclinical studies of cellular and animals models have supported the beneficial effects of ALCAR in depression. ALCAR showed reduced immobility time of rats in forced swim test(60). Many studies have proposed diverse mechanism of action of ALCAR in depression treatment even though the exact mechanism is still unknown. Neuroplasticity effect, membrane modulation and neurotransmitter regulation are well studies potential mechanism among many.

Neuroplasticity effects

Recently, hippocampal neurogenesis increase is widely implicated as a mechanism of many anti depressants. Animal studies suggest that the induction of neuroplasticity and neurogenesis in the brain is the cause for the behavioural effects of chronic anti depressants)(61). Epigenetics is known to play an important role in the pathophysiology of major depression. Epigentics is the most important part of neuroplasticity(58). The function and expression of mglu2/3 receptors were reduced in the hippocampus of depressed rat. When the mglu2/3 receptors were activated the time for the therapeutic efficacy of the antidepressants were shortened(62).

With consideration of these results, ALCAR produced rapid anti depressant activity than chlorimipramine via epigenetic induction of mglut2 receptors (9). ALCAR also causes acetylation in nfkb binding sites (44). This causes the upregulation of mglu2 levels via gene transcription of GRM2 and neurogenesis promotion in the hippocampus and prefrontal regions increasing the efficacy of anti depressants. (Cuccurazzu et al., 2013; Nasca et al., 2013)(9,63).

Neutotrophic factors dysregulation can have a negative impact on the neuroplasticity causing depression. (Hayley et al., 2005). The neurotrophic factors like brain derived neurotrophic factor(BDNF), glial cell line derived neurotrophic factor(GDNF), insulin-like growth factor 1 (IGF-1), nerve growth

factor (NGF), and vascular endothelial growth factor (VEGF) are all reduced in concentration in depression(58). A study in the rat brain revealed that the repeated ALCAR could prevent stress induced decrease in nerve growth factor (65). Another study also revealed that the increase in the other neurotrophic factors like BDNF,GDNF family ligands in hippocampus. Spinal cords and pre frontal cortex along with dose dependantanti depressant effect in forced Swim test in animal models of depression(66).

Common Membrane Mechanisms

Alterations in the lipid and membrane molecular metabolism play a vital role in the pathophysiology of depression(67).low levels of cholesterol and omega 3 fatty acid deficiencies are found to be associated with higher incidence of depression(68). ALCAR improved the levels of myo inositol and delays the development of myo inositol deficiency in rat with diabetic neuropathy(69). A study hypothesis is based on this fact that ALCAR, myo-inositol, omega-3 fatty acids, and lithium all exhibit anti depressant effect through effect on membrane phospholipid metabolism and membrane physical chemical properties(70).

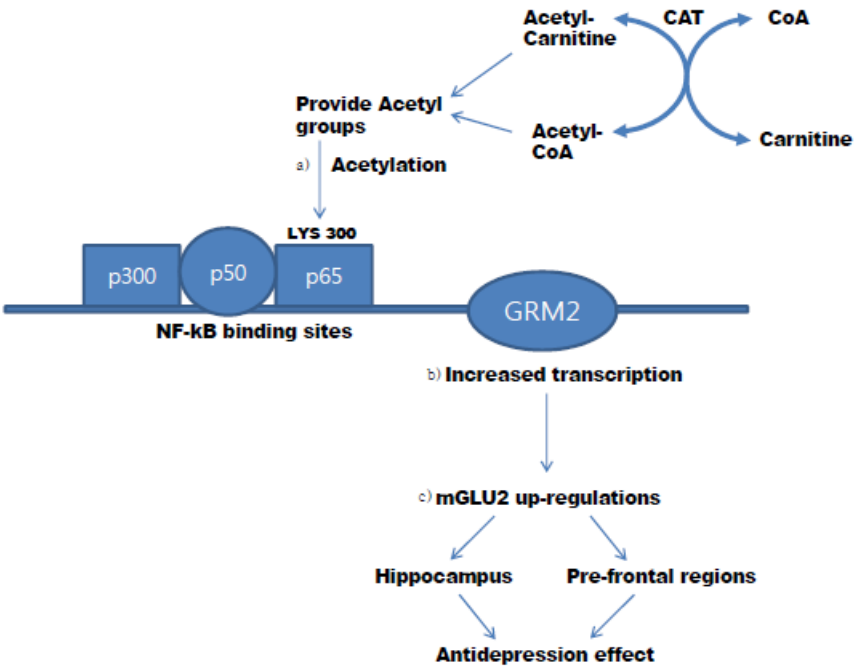

Figure 14: Putative mechanism of ALCAR induced antidepressive effect via improving neuroplasticity.

a) ALCAR provided acetyl groups cause acetylation of p65 at LYS (310) located in NF-κB binding sites.

b) Transcription of GRM2

c) Upregulation of mGLU2 and promotions of neurogenesis in hippocampus and pre-frontal regions.

CAT – carnitineacetyltranslocase, mGLU2 – type 2 metabotropic glutamate receptors.

Neurotransmitter regulations

Mono amine hypothesis has been a predominant pathology of depression(10). ALCAR increases the level of 5-hydroxyindolacetic acid (5HIAA) which is a metabolite of serotonin. A study proved the potential agonistic action of 5 HT1A receptors(64). Another study showed that the chronic ALCAR reported to increase 5HT in cereberal cortex and reduced serotonin turnover by decreasing 5-HIAA/5HT ratio(71). Also long term ALCAR found to enhance dopamine and serotonin output in mesocorticolimbic areas and acute stress protection(72).

OTHER USES

1. Hepatic encephalopathy
2. Male infertility (asthenospermia)
3. Multiple sclerosis-related fatigue
4. Peyronie's disease
5. Sciatica
6. Chronic cerebral ischemia Alcoholism
7. Alzheimer's disease.
8. Amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease)
9. Fibromyalgia.

Contraindications

Cirrhosis, High blood pressure, Digestive problems, Hepatitis C, Peripheral vascular disease, breathing problems, Sleeping problems, Kidney failure (73).

Bersani et al in his study used Acetyl-L-carnitine 1g t.i.d daily orally for 8 weeks in 80 patients with dysthymic disorder patients showed a statistically significant improvement over placebo in the following scales: HAM-D, HAM-A, BDI and ToulusePieron Test. So in this study we used 500mg twice daily oral dose of Acetyl-L-carnitine in patients with depression to see the efficacy and tolerability.

Depression as a disorder needs newer, rapidly acting efficacious treatment. The standard treatment available cause many adverse effects and has minimal latency period of 2 weeks. This study will add a oral drug that has minimal side effects and decrease in the latency period for treatment response in patients with Depression. Though few studies are available regarding the efficacy of Acetyl -L-carnitine in depression, no study data available regarding the use in Indian population. Hence the study has been planned to be conducted in our tertiary care hospital.

AIM & OBJECTIVES

AIM

- To study the efficacy and safety of Acetyl L-Carnitine in the treatment of patients with depression.

OBJECTIVES

1. To study the efficacy of Acetyl L-Carnitine as an add-on therapy in the treatment of depression as compared to the standard treatment.
2. To assess and compare the latency period with Acetyl L-Carnitine as an add on therapy with antidepressants.
3. To study the safety profile of Acetyl L-Carnitine

MATERIALS AND METHODS

The study was a prospective, open label; randomized controlled study. This study was conducted at the out-patient department (OPD) of Psychiatry, Kilpauk Medical College, Chennai from June 2019 to May 2020.

Approval from the Institutional Ethics Committee was obtained prior to the commencement of the study. The study was conducted according to the guidelines laid down by ICMR on the conduct of biomedical research.

Study group: Patients diagnosed newly with Depression in Psychiatry Out-Patient Department are included in this study.

Study design: Prospective, open label, randomized controlled study

Study duration: One year.

Study Period: June 2019 to May 2020.

SAMPLE SIZE

The sample size for this study was calculated with the help of Open Epi software, Version 3. The power of the study was set at 80%, with two side confidence interval at 95%. The outcome was to assess the difference of 5 in the mean score ofMontogomery&Asberg Depression Rating Scale (MADRS) from Baseline between 2 groups and Standard deviation of 7. The Sample Size was calculated to be 31 patients in each group total of 62 patients.

SCREENING

The study procedure required screening for patients with newly diagnosed depression, from those who attended out-patient department of the hospital. Conformation of the diagnosis of Depression was done by detailed history, clinical examination by the Psychiatrist at the OPD department of Psychiatry. The severity of depression was assessed by Montogomery-Asberg Depression rating scale (MADRS) by the Psychiatrist.

SELECTION CRITERIA:

Inclusion criteria:

1. Patients newly diagnosed with depression.
2. Patients of both sex.
3. Age 18-65 years

Exclusion criteria:

1. Pregnant and Lactating mothers.
2. Hypothyroidism.
3. Patients with renal failure.
4. Patients with seizure disorder.
5. Patients who have received Electro Convulsive Therapy (ECT)
6. Patients diagnosed with bipolar depression.
7. Patients who lack capacity to give consent.

STUDY PROCEDURE

The study was conducted after Institutional Ethical Committee approval. Patients who fulfilled the selection criteria were recruited for the study. The study was conducted according to good clinical practice guidelines. Written informed consent was obtained from all patients, in regional language in the prescribed format and explained about the study purpose and procedures prior to their enrollment in study. In patients who were illiterate, the study procedure and their right to withdraw or contact the principal investigator in case of any side effects was explained and left thumbimpression was obtained.

RANDOMIZATION

Computer based randomization table was used to randomize the patients. Patients diagnosed with depression and those willing to participate in the study were randomized equally with the help of random numbers table into 2 groups.

Table 4: The Study Groups with Sample Size and Treatment Protocol

Control Group	ALCAR Group
n = 31	n = 31
Patients received standard treatment for 12 weeks	In addition to standard treatment, received Acetyl-L-Carnitine for 12 weeks.

Group 1- Standard treatment for depression consists ofSSRIs (sertaline 50mg/escitalopram 20mg) as per diagnosis by the Psychiatrist.

Group 2– Received treatment consists of T.Acetyl L Carnitine 500 mg twice a day along with standard treatment which includes SSRIs (sertaline 50mg/escitalopram 20mg), for 3 months.

ASSESSMENT OF PARTICIPANTS

A detailed history was obtained from every patients included for the study. General examination, vital signs and systemic examination were assessed on these patients. The findings were noted in the case report form (CRF).

STUDY PROCEDURE

A total of 62 patients diagnosed with depression were included in the study. Following screening and brief explanation about the study and getting informed consent, they were randomised into two groups. The following investigations were done to all patients before initiation of therapy and at the end of 3 months for all participants - Complete blood count, Lipid profile, Random blood sugar, serum creatinine, urea, TSH to rule out any co morbidities.

These patients had 2 check-ups.

1st check-up: Patients were asked to review with detailed history, clinical examination and investigation results by the Psychatrist.

2nd check-up: After conformation of the diagnosis, randomization was done. The severity of depression was assessed by Montogomery&Asberg Depression rating scale (MADRS) by the Psychiatrist. Then respective treatment was initiated in both groups.

Participants in both the groups were followed up five times.

At the end of 1st,2nd,4th,8th and 12th week from the initiation of treatment - Patients in both groups were assessed for improvement of symptoms by using Montogomery&Asberg Depression rating scale (MADRS). They were also enquired for side effects and general examination was done at each visit.

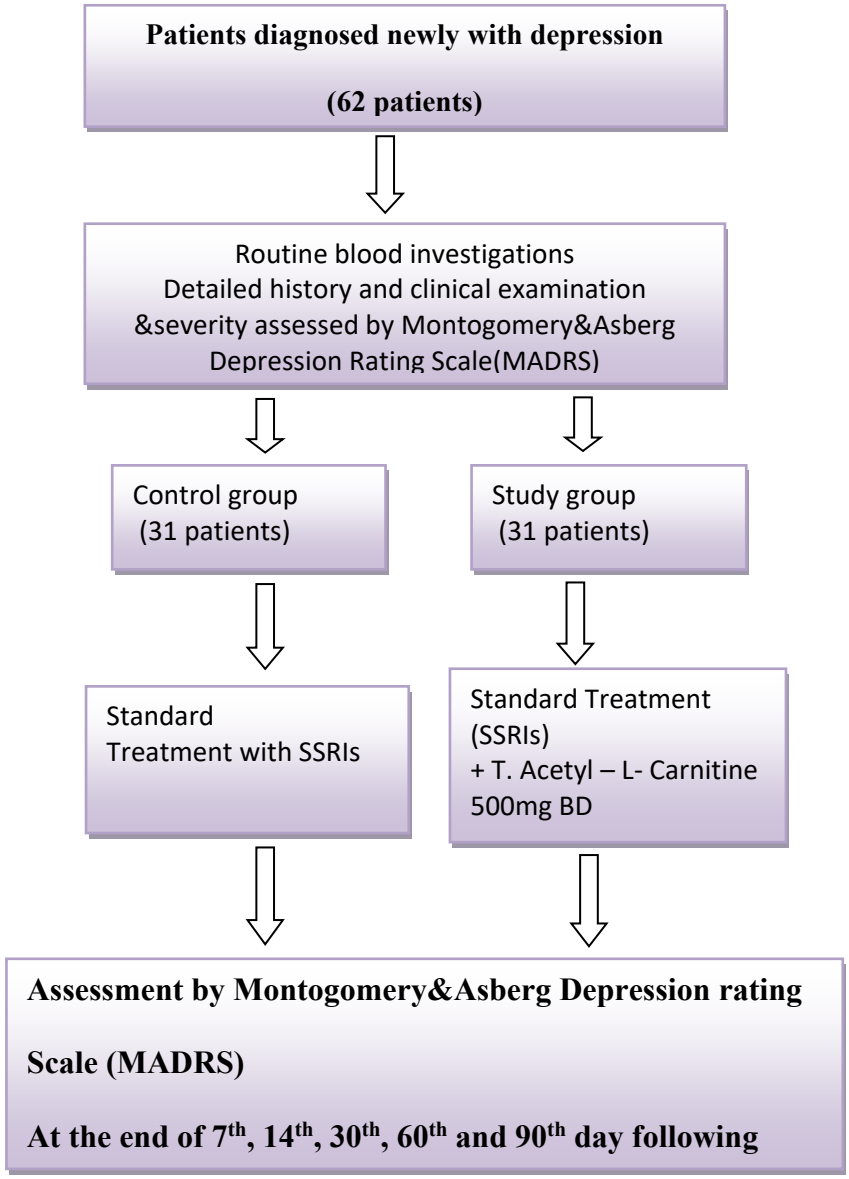

Figure 15: Flow Chart Of The Study Methodology

STATISTICAL ANALYSIS

Statistical analysis was done by using **SPSS** software, version 21.0.Analysis of efficacy was done by per protocol analysis. Variables (Montogomery&Asberg Rating scale) expressed in mean ± standard deviation were analysed by **t test**. Intra group analysis was done by **paired t-test**, inter group analysis was done by **unpaired t test**. Repeated measures of **ANOVA** were also used for intra group and inter group analysis.

RESULTS

Patients attending the psychiatric OPD were screened for depression according to clinical history and Montogomery-Asperg Rating Scale(MADRS). Out of the 70 subjects who were screened, 62 patients satisfied the inclusion criteria. These patients were randomized and equally distributed between the Control (n=31) and ALCAR (n=31) groups. There were 2 drop outs in the ALCAR group (patients who didn't come for follow up or discontinuation of drugs due to adverse effects) and 2 drop out in control group (patients who didn't come for follow up) respectively, leading to 29 patients in the ALCAR group and 29 in the Control group.

DEMOGRAPHIC DATA

There were no significant differences between the baseline characteristics of patients in the two groups.

Table 5: Comparison of Mean Age in Years between ALCAR and CONTROL Group

Parameters	ALCAR group Mean± SD	Control group Mean± SD
Age (years)	39.47±13.52	40.17±13.77

The table shows the comparison of mean age in years between the study groups. The ALCAR group had a mean age of 39.47 ± 13.52 and the CONTROL group with a mean age of 40.17±13.77. The difference in age between two groups showed no statistical significance.

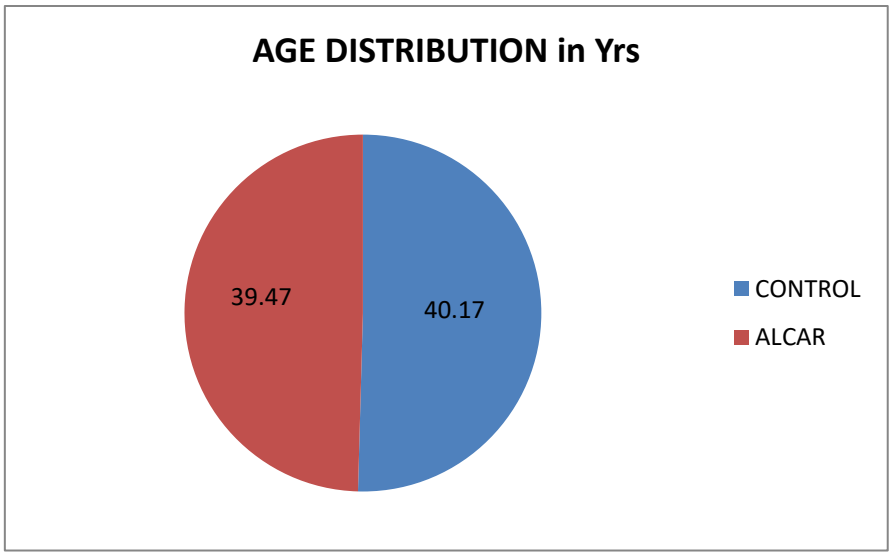

Figure 16: Comparison of Age in years between ALCAR and Control group

The pie chart shows the comparison of mean age in years between the ALCAR group and Control group.

Table 6: SEX DISTRIBUTION AMONG ALCAR AND CONTROL GROUP

GENDER	ALCAR group n	Control group n
MALE	15	16
FEMALE	14	13

Among 29 patients in control group 55.17% (n=16) were male. Out of 29 patients in ALCAR group 51.73% (n=15) were male. There was almost equal number of male:female ratio in both the study groups.There was no statistical significance between the groups regarding sex distribution.

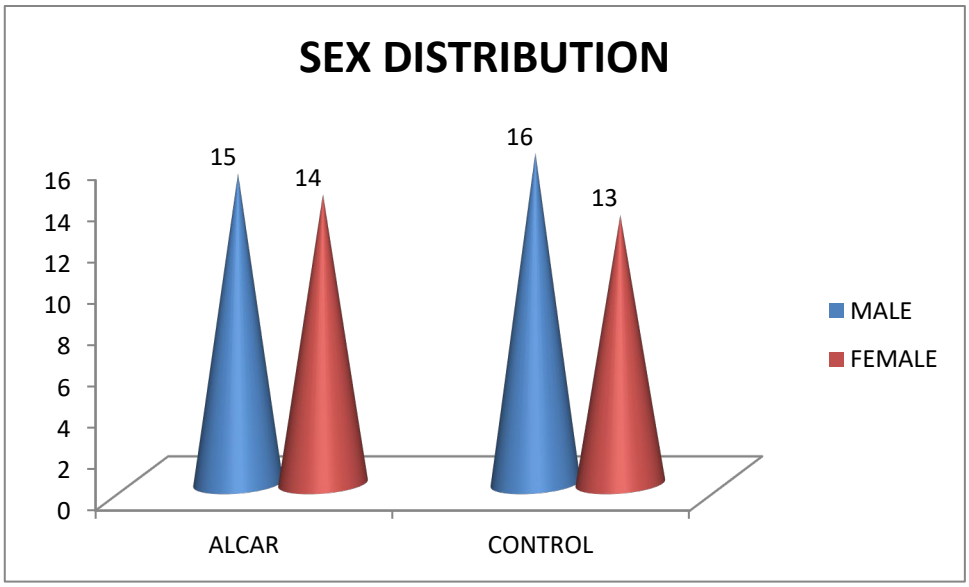

Figure 17: Comparison of Sex distribution between ALCAR and Control group

The clustered cone column shows the sex distribution between the ALCAR and Control group. The ALCAR group included 15 male and 14 female subjects and the Control group with 16 male and 13 female subjects.

Table 7:Distribution of Depression Severity Between ALCAR And Control Group using MADRS score

SEVERITY	ALCAR group n	CONTROL group n
Moderate	19	18
Severe	10	11

The table shows the distribution of depression severity in both the study groups using MADRS score. In the ALCAR group, 19 subjects were found to

have moderate depression and 10 subjects with severe depression. In the Control group, 18 subjects were found to have moderate depression and 11 subjects with severe depression.

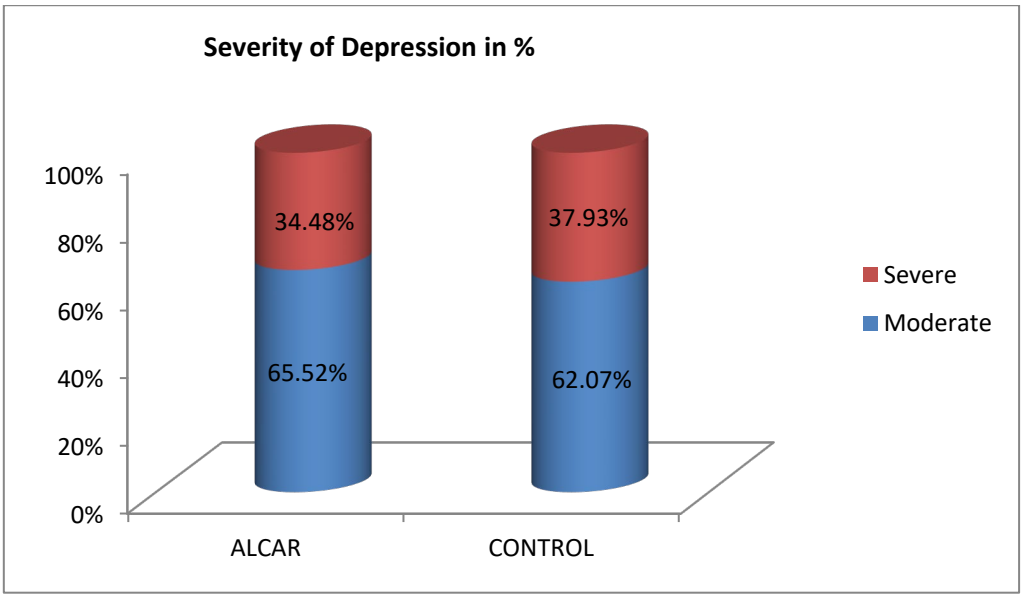

Figure 18: Comparison of Severity of Depression in percentage between ALCAR and Control group.

The above figure shows the severity of depression in percentage using MADRS score in both the study groups. Baseline Severity assessment of depression shows similar distribution and comparable between group ALCAR and Control.

Table 8:Comparison of mean values of MADRSamong the study groups between baseline and at the end of 1st week.

Groups	BASELINE Mean± SD	1st week Mean± SD	p value
Control	35.07± 6.58	33.55± 5.89	0.36
ALCAR	36.97± 7.63	27.45± 5.28	<0.001***

$p \leq 0.05^{*}$ is significant; $p \leq 0.01^{**}$ is highly significant; $p \leq 0.001^{***}$ is very highly significant

The table compares the mean values of MADRS score between the study groups at the baseline and at the end of 1st week. The mean value of the MADRS score between both groups showed reduction when compared to baseline. The mean value of the score in the ALCAR group showed a very highly statistical significance between the baseline and at the end of 1st week with a p value $<0.001^{***}$, whereas the control group showed no statistical significance.

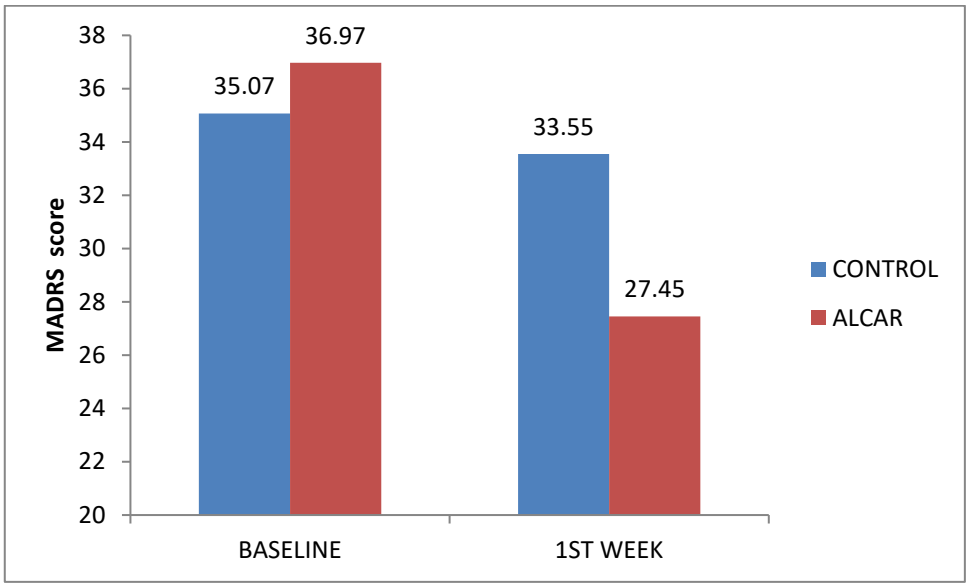

Figure 19: Comparison of mean value of MADRS score at baseline and at the end of 1st week between ALCAR and Control Group

The bar diagram shows the MADRS score at baseline and at the end of 1st week between ALCAR and Control Group. The ALCAR group had a mean score of 36.97 at baseline and 27.45 at the end of 1st week with a p value of $<0.001^{***}$(very highly significant). The Control group had a mean score of 35.07 at baseline and 33.55 at the end of 1st week with a p value of 0.36 (no statistical significance).

Table 9:Comparison of mean values of MADRS score between ALCAR and Control group at different time period.

TIME OF ANALYSIS	Montogomeryasberg Depression Rating Scale (MADRS)		pVALUE
	MEAN±*SD*		
	Control	ALCAR	
BASELINE	35.07±6.58	36.97±7.63	0.16
At the end of 2nd week	26.17±6.74	25.72±4.96	0.39
At the end of 4thweek	26.17±6.74	21.59±4.59	<0.01**
At the end of 8thweek	22.69±5.34	19.97±2.67	<0.01**
At the end of 12thweek	22.69±5.33	19.42±2.23	<0.01**

p≤0.05* is significant; p≤0.01** is highly significant; p≤0.001*** is very highly significant

The table compares the mean MADRS score between ALCAR and Control group at different time periods. The meanMADRS score was significantly reduced in 2nd week compared to baseline in both groups. The meanMADRS score between the two groups at 2nd week was not statistically significant. The mean MADRS score was reduced in 4th, 8th and 12th week when compared to baseline in both the groups. The mean MADRS score between ALCAR and Control group at 4th,8thand 12th week was found to be statistically significant with p value<0.01*.

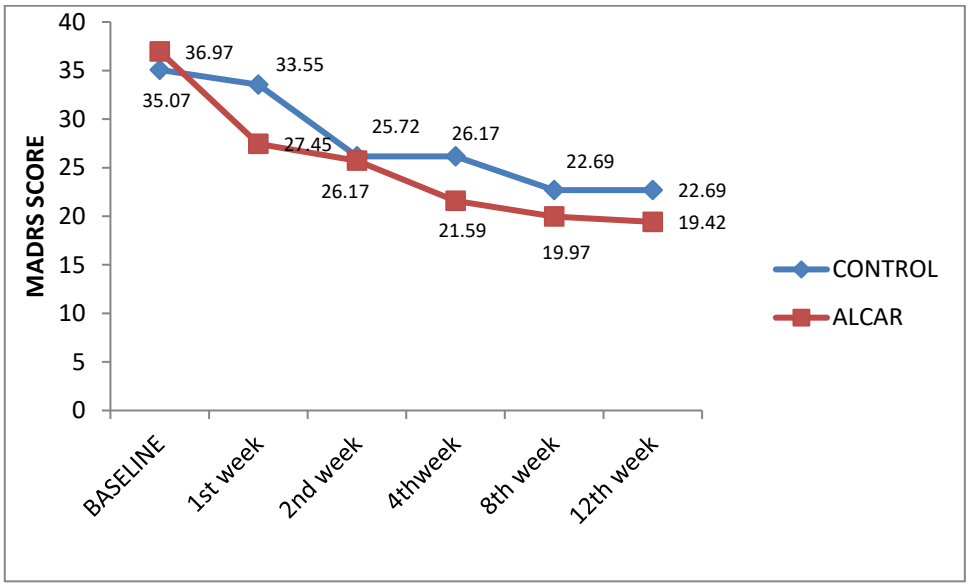

Figure 20: Graph comparing MADRS score between ALCAR and Control group at different time periods.

The graph shows a steady decline in MADRS score in both the groups from baseline till 12th week. Reduction in MADRS score was more in ALCAR group when compared with the Control group from baseline till 12th week.

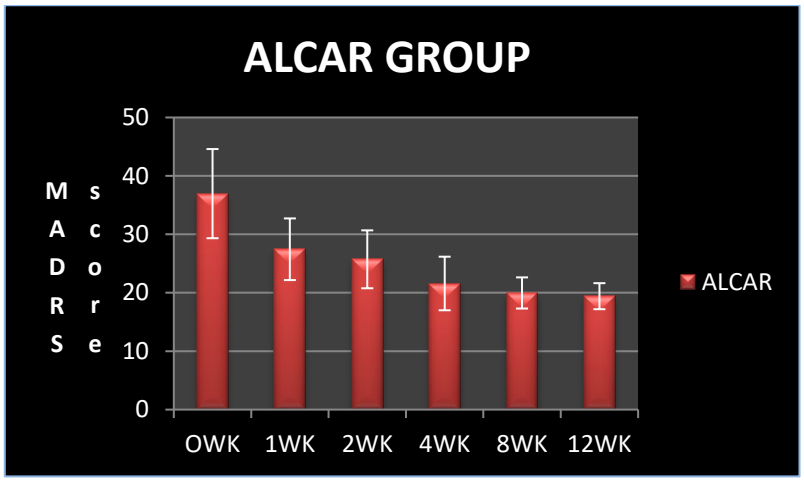

Figure 21: Comparison of MADRS score in the ALCAR group at different periods.

The chart shows comparison of MADRS score in the ALCAR group from baseline till 12th week. There is a reduction of MADRS score in the ALCAR group from the baseline till 12 week.

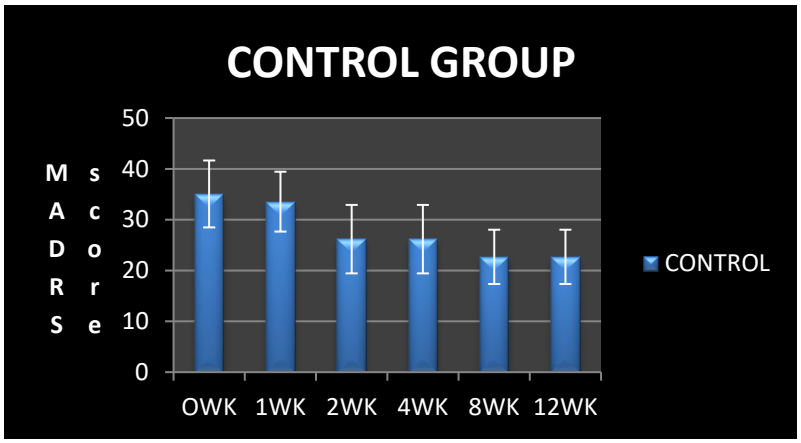

Figure 22: Comparison of MADRS score in the Control group at different periods.

The chart shows comparison of MADRS score in the Control group from baseline till 12th week. There is a reduction of MADRS score in the Control group from the baseline till 12 week.

Table 10:Comparison of mean value of MADRS score between Sertaline and Escitalopram in ALCAR group

ALCAR group			
	SERTALINE (n=12)	**ESCITALOPRAM (n=17)**	**p VALUE**
BASELINE	35.83±7.53	37.657±7.94	0.54
1st week	27.**75** ±4.58	27±5.98	0.71
12th week	19.92±2.15	19.297±2.02	0.44

$p \leq 0.05^{*}$ is significant; $p \leq 0.01^{**}$ is highly significant; $p \leq 0.001^{***}$ is very highly significant

The table shows the comparison of MADRS score in ALCAR group with Sertaline and Escitalopram at baseline, 1st week and 12th week. When compared between Sertaline and Escitalopram in the ALCAR group, the p value was statistically not significant at baseline, 1st week and 12th week.

Table 11: Adverse events between ALCAR group and Control group

ADVERSE EVENTS	ALCAR GROUP	PERCENTAGE	CONTROL GROUP	PERCENTAGE
Nausea	4	13.70%	1	3.40%
Vomiting	2	6.80%	0	
Diarrhea	0	0	1	3.40%
Loss of appetite	1	3.40%	1	3.40%
Weight gain	2	6.80%	1	3.40%
Hairfall	2	6.80%	0	
Insomnia	2	6.80%	2	6.80%
Headache	0	0	1	3.40%

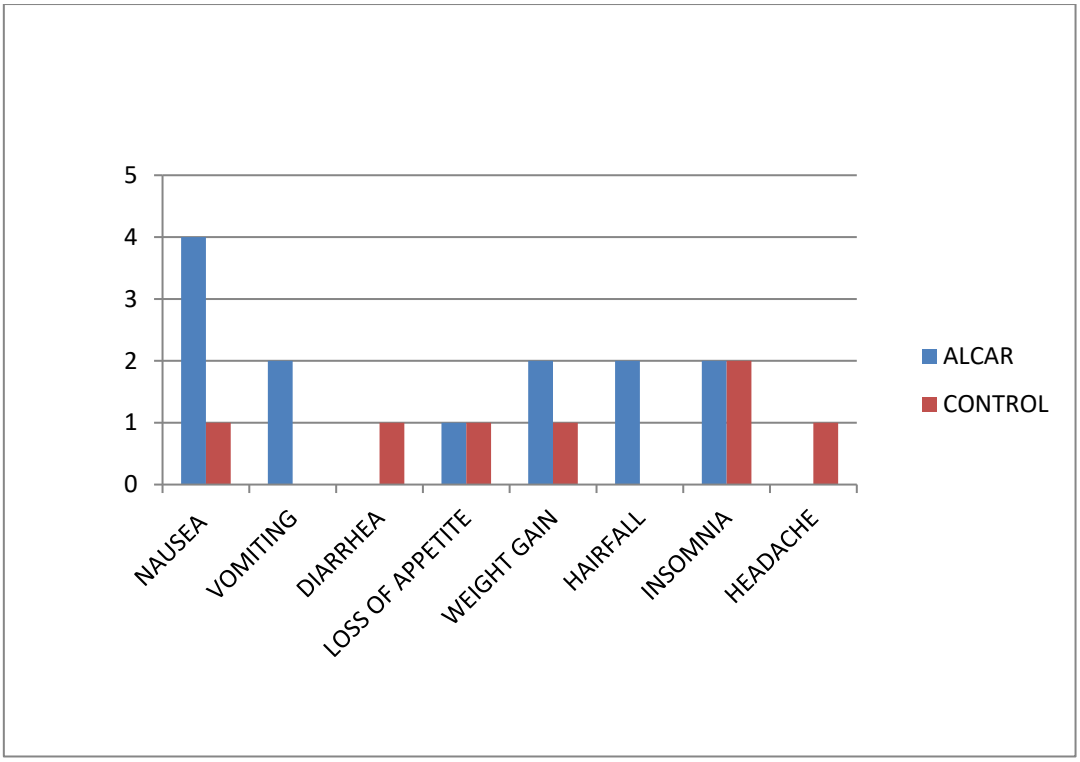

Figure 23: Comparison of adverse effects between ALCAR group and Control group.

The table and figure shows the comparison of adverse drug reaction between ALCAR and Control groups. Most of the ADR were comparable in both the groups. ADRs like loss of appetite and insomnia occurred were similar in both ALCAR and control group, whereas gastrointestinal adverse effects like nausea, vomiting and weight gain were seen more in ALCAR group than the Control group. Noticeable adverse effect with ALCAR was hairfall, Whereas some disturbing ADR like headache and diarrhea were not seen in ALCAR in comparison with the control group.

DISCUSSION

Depression is the most common of all psychiatric illnesses. The diagnosis of Depression mainly depends on clinical history,mental state examination and Depression rating scale findings. We enrolled sixty two patients for our study and randomized into two groups with thirty one in each group (Control group,ALCAR group). Control group received treatment with SSRIs (Escitalopram or Sertaline). ALCAR group received Acetyl-L-Carnitine along with SSRI.

The beneficial effects of ALCAR in Depression are supported in numerous cellular,animal and human studies with varied results.

Acetyl-L-Carnitine(ALCAR) decreased the immobility time of rats in forced swim test(60).Even though exact action is unknown in the treatment of Depression, the most potential mechanism include neuroplasticity,membrane modulation and neuro transmitter regulation. The result from the animal study has proved the role of ALCAR's beneficial effect in Depression. In terms of neuroplasiticity, one significant hypothesis is that ALCAR may promote neurogenesis in the hippocampus and prefrontal regions via upregulation of mGLU receptors caused by NF-kB p65 Acetylation(6,63) . ALCAR may also exhibit antiDepressant effects via increasing neurotrophic factors including BDNF, ARTN, and NGF(66)(65). Alteration of membrane molecular and lipid metabolism is one more important pathophysiology of Depression(67)and ALCAR may also increase myo-inositol level and improve brain energy

metabolism via alterations in glucose and lactate metabolism as well as increases in high energy phosphates and myo-inositol(69). Its effect in neurotransmitter regulations, especially serotonergic and possibly dopaminergic activities, could also contribute to antidepressant actions(64,71).

Various studies have compared the incidence of depression in various age groups which found that it is more prevalent in later part of life (21) whereas in our study the mean age group was 39.47 years in ALCAR group and 40.17 years in Control group and there was no statistical significant difference in mean age between the two groups. The prevalence of Depression is common in females than males (7) but in our study there was no specific gender predominance was seen. Hence no statistically significant difference was observed between both sexes.

The dosing concentrations of Acetyl L-Carnitine are heterogeneously reported, with the most commonly reported dosing in mg/kg in most of the animal studies(63,74).Human studies tend to report the regime as mg/d dosing with no studies titrating to weight. There is a large variability in the dosing ranging from 500 to 3000 mg/d among various studies(64,75). The daily dose of 1g/day was defined on basis of previous clinical studies in Dysthmic disorders(76). Recent bio availability studies shown that ALCAR absorption is dose limited and does not increase significantly above the total daily dose of 1gm/day(76). Also ALCAR was found to be equally tolerable to placebo and more tolerable than some anti Depressants like Fluoxetine and Amisulpride by Bersani et al., 2013.

The assessment of outcome in previous studies was targeted mainly on reducing Depressive symptoms and overall clinical improvement based on various scales for Depression. In our study we considered the outcome of reduction in score for MontogomeryAsberg Depression Ration Scale and reduction in Depressive symptoms and to monitor the adverse effects of ALCAR. A strong association of ALCAR deficiency and MDD has been focused in a previous study (77).

First randomized study done by Villardita*et al*. was double blind,placebo controlled study to study the clinical efficacy of ALCAR on patients with Depression ; The results showed that ALCAR was superior to placebo. Bella et al., studied elderly patients diagnosed with DSM-III-R Dysthmic disorder showed that ALCAR was statistically superior to placebo. An identical study conducted by Fulgente et al., included patients with DSM-III-R Dysthmic disorder with mean HDS-17 score for the ALCAR group also showed superior outcome compared with placebo group .

Effect of ALCAR by Cavallini et al, in patients with diverse medical illness, having no mood disorder but Depressive symptoms was studied. This study compared the efficacy of Carnitine, testosterone undecanoate (TUT), and placebo in elderly patients with Depressive symptoms, The effects of these three agents on Depressive symptoms were compared using Hamilton Depression and Melancholia Scale (HDMS), and the results showed that HDMS scores were significantly lower than that of TUT group’s .

Malaguarnera et al,studied ALCAR's superior antidepressant efficacy in patient's with minimal hepatic encephalopathy,there was significant lower scores in mean BDI and State-trait anxiety inventory (STAI) scores in the ALCAR group than in the placebo group .

Martinotti et al study evaluated the efficacy of ALCAR on anhedonic symptoms of patients with (detoxified) alcohol dependence outcome measure were mean change of anhedonic symptoms resulted in significantly greater reduction ALCAR group with respect to placebo. ALCAR was also effective in improving Depressive symptoms of fibromyalgia patients and minimal hepatic encephalopathy by Malaguarnera et al., Rossini et al. Recent controlled clinical trials by Ciacci et al., Cruciani et al., have proved its effect on improvement of fatigue in various medical disorders as well as also showing potential beneficial effects in reducing pain in fibromyalgia. A study by Brennan et al.,in bipolar Depression failed to demonstrate a significant treatment effect for ALCAR over placebo

ALCAR's clinical efficacy in patients with Depression, Dysthmic disorder, and its superior efficacay over placebo in patients with Dysthmic disorder was also shown in studies by Bella et al., and Fulgente T., Other studies by Bersani et al., Zanardi and Smeraldi, further showed that ALCAR is as equally effective as Fluoxetine and Amilsulpride in patients with Dysthmic disorder, which was similar to our study . In our study there was a significant

mean reduction seen in both ALCAR group and control group at 4th week,8th week and 12th week when compared to baseline.

In our study at 1stweek significant reduction in mean percentage of MADRS score in ALCAR group at 1st week when compared to control group. The p value(<0.001) was highly significant ALCAR group when baseline and 1st week score was compared which demonstrated the reduction in the latency period with ALCAR treatment when compared to SSRIs alone.

When 2nd week mean value was compared between ALCAR and control group it was not significant statistically which may be due to the therapeutic effect of anti depressants after the latency period from the initiation of the treatment.

In a study by Bersani et al. in patients with Dysthmic disorder exhibited similar findings of mean reduction in 2nd week showed same results in both Amisulpride treated patients and ALCAR treated patients .The value was highly significant statistically when the mean value at 4th week,8th week and 12th week of the ALCAR and control group was compared (p value = <0.01), which denotes that the patients treated with ALCAR has higher reduction in MADRS score and disease severity when compared to patients treated with anti depressants alone.

Even though previous studies by Zanardi et al,Bersani et al proved the anti depressant effect of ALCAR there are no previous studies were done to see any additive effect of anti depressants along with ALCAR. In our study when the mean values of control and ALCAR were compared at the end of 12th week there was significant reduction of MADRS scores in the ALCAR group when compared to the control group (p value = <0.01), so it is safe to conclude the ALCAR when combined with anti depressants exhibit an additive effect.

THE ASSESSMENT OF LATENCY PERIOD IN BOTH GROUPS.

Analysis of latency period in both groups revealed that there was reduction in the latency period with ALCAR treatment (ALCAR + Sertaline or Escitalopram) when compared to control group (either Sertaline or Escitalopram). The latency period was reduced to one week in ALCAR group when compared to control group which showed 2 week for therapeutic response. when the mean values of MADRS at 1st week of ALCAR and control group was compared it was highly significant statistically(p value <0.001) ,which specifies that the therapeutic response was seen 1 week earlier when compared to control group in ALCAR treated patients. A study by nasca et al demonstrated that the epigenetic regulation of type 2 metabotropic (mGlut2)receptor s caused rapid and long ;asting antidepressant effect. The rapid onset of action of ALCAR was demonstrated in our study as suggested by the Nasca et al., thereby the involvement of mGlut2 in pathogenesis of Depression should be investigated by further research for better understanding and targeted treatment of the illness.

ASSESSMENT OF OUTCOME BETWEEN 2 ANTI DEPRESSANTS IN ALCAR GROUP

In our study 2 antidepressants (either Sertaline or Escitalopram) were used along with ALCAR.We compared the values of mean reduction between the two antidepressants in ALCAR group as to asses a better outcome with either drug. There was no statistical difference when the scores in Sertaline and Escitalopram group was compared at 1st and 12th week. So it may be considered that it has over all improvement used with any SSRIs rather than a specific drug. Further studies need to be done with other SSRIs to prove this point.

ADVERSE DRUG REACTIONS IN BOTH GROUPS

The adverse reactions reported were only mild and there was no serious adverse drug reactions noted in our study. The most common adverse effects in study group was nausea followed by vomiting,weight gain and hairfall. Nausea,vomiting and weight gain can be associated with ALCAR because the severity of these symptoms were less in control group. Additionally the routine investigations like Complete blood count, Lipid profile, Random blood sugar, serum creatinine, urea, TSH were done before and after the treatment period revelaed no abnormality in any of the parametes and all the values were well within normal limits. so we can safely conclude that ALCAR is generally tolerable and safe when compared to anti Depressants as most of the adverse effects were mild gastro intestinal symptoms .

CONCLUSION

From this study we conclude that,

1. Acetyl-L-Carnitine at dose of 1gram/day as anadd on therapy with SSRIs is effective in improving the overall symptoms of Depression.
2. It causes rapid onset of Antidepressant effect by reducing the latency period to 1 week, whereas SSRIs took 2 week to achieve the therapeutic effect.
3. It is safe in patients with Depression as an add on therapy to SSRIs as only minor gastrointestinal symptoms were reported as adverse reaction in ALCAR group.
4. Further studies are needed to explore the long term efficacy of Acetyl-L-Carnitine in the treatment of Depression.

BIBLIOGRAPHY

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. (2018). Global, reg

ional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. DOI.

2. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global Burden of Disease and Risk Factors. Washington: The World Bank; 2006.

3. Preskorn SH (2012) Ketamine: The hopes and the hurdles. Biol Psychiatry 72(7):522–523.

4. Rush AJ, et al. (2009) STAR*D: Revising conventional wisdom. CNS Drugs 23(8):627–647.

5. Barhwal K, et al. (2009) Acetyl-L-carnitine (ALCAR) prevents hypobaric hypoxia-induced spatial memory impairment through extracellular related kinase-mediated nuclear factor erythroid 2-related factor 2 phosphorylation. Neuroscience 161(2):501–514.

6. Nasca C, Bigio B, Lee FS, Young SP, Kautz MM, Albright A, et al.

8. Schroeder FA, Lin CL, Crusio WE, Akbarian S (2007) Antidepressant-Acetyl-l-carnitine deficiency in patients with major depressive disorder. Proc Natl Acad Sci. 2018 Aug 21;115(34):8627–32.

7. Tsankova N, Renthal W, Kumar A, Nestler EJ (2007) Epigenetic regulation in psychiatric disorders. Nat Rev Neurosci 8(5):355–

367. 9 Schroeder FA, Lin CL, Crusio WE, Akbarian S (2007. like effects of the histone deacetylase inhibitor, sodium butyrate, in the mouse. Biol Psychiatry 62(1):55–64.

9. Nasca C, Xenos D, Barone Y, Caruso A, Scaccianoce S, Matrisciano F, et al. L-acetylcarnitine causes rapid antidepressant effects through the epigenetic induction of mGlu2 receptors. Proc Natl Acad Sci. 2013 Mar 19;110(12):4804–9.

10. Massart R, Mongeau R, andLanfumey L. Beyond the monoaminergic hypothesis: neuroplasticity and epigenetic changes in a transgenic mouse model of depression. Philos Trans R SocLond B BiolSci 2012; 367: 2485-2494.

11. Bauer M, Pfennig A, Severus E, Whybrow PC, Angst J, Moller HJ, andSon behalf of theTask Force on Unipolar Depressive D. World Federation of Societies of BiologicalPsychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar DepressiveDisorders, Part 1: Update 2013 on the acute and continuation treatment ofunipolar depressive disorders. World J Biol Psychiatry 2013; 14: 334-385.

12. Ferrari F, Gorini A, Villa RF. Functional proteomics of synaptic plasma membrane ATP-ases of rat hippocampus: effect of l-acetylcarnitine and relationships with Dementia and Depression pathophysiology. Eur J Pharmacol. 2015 Jun 5;756:67-74.

13. Organization WH, others. Depression and other common mental disorders: global health estimates. 2017 [cited 2017 Jul 5]; Available from: http://apps.who.int/iris/bitstream/10665/254610/1/WHO-MSD-MER-2017.2- eng.pdf.

14. Kessler RC, Bromet EJ. The Epidemiology of Depression Across Cultures. Annu Rev Public Health. 2013 Mar 18;34(1):119–38.

15. Grover S, Dutt A, Avasthi A. An overview of Indian research in depression. Indian J Psychiatry. 2010 Jan 1;52(7):178.

16. Reddy MS. Depression: The Disorder and the Burden. Indian J Psychol Med. 2010;32(1):1–2.

17. Causes of Depression [Internet]. WebMD. [cited 2017 Jul 4]. Available from: http://www.webmd.com/depression/guide/causes-depression.

18. Philippi CL, Motzkin JC, Pujara MS, Koenigs M. Subclinical depression severity is associated with distinct patterns of functional connectivity for subregions of anterior cingulate cortex. J Psychiatr Res. 2015 Dec 1;71:103–11.

19. Gelder, M., Andreasen, N., Lopez-Ibor, J., & Geddes, J. (Eds.). New Oxford Textbook of Psychiatry. Oxford,. UK: Oxford University Press.;

20. Oakes P, Loukas M, Oskouian RJ, Tubbs RS. The neuroanatomy of depression: A review. Clin Anat. 2017 Jan 1;30(1):44–9.

21. Trevor BGKAJ, Katzung BG. Basic and Clinical Pharmacology 13th/2015. Mc Graw Hill; 2015.

22. New Oxford Textbook of Psychiatry.

23. Niraj Ahuja. A Short Textbook of PSYCHIATRY. Seventh Edition. JAYPEE BROTHERS MEDICAL PUBLISHERS (P) LTD;

24. Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct Funct. 2008 Sep;213(1-2):93–118.

25. Gautam S, Jain A, Gautam M, Vahia VN, Grover S. Clinical Practice Guidelines for the management of Depression. Indian J Psychiatry. 2017 Jan;59(Suppl 1):S34–50.

26. Lewinsohn PM, Rohde P, Seeley JR. Major depressive disorder in older adolescents. Clin Psychol Rev. 1998 Nov 1;18(7):765–94.

27. Larson SL, Owens PL, Ford D, Eaton W. Depressive Disorder, Dysthymia, and Risk of Stroke: Thirteen-Year Follow-Up From the Baltimore Epidemiologic Catchment Area Study. Stroke. 2001 Sep 1;32(9):1979–83.

28. Wulsin LR, Singal BM. Do Depressive Symptoms Increase the Risk for the Onset of Coronary Disease? A Systematic Quantitative Review. Psychosom Med. 2003 Apr;65(2):201–10.

29. Wulsin LR, Vaillant GE, Wells VE. A Systematic Review of the Mortality of Depression. Psychosom Med. 1999 Feb;61(1):6–17.

30. Vahia VN. Diagnostic and statistical manual of mental disorders 5: A quick glance. Indian J Psychiatry. 2013;55(3):220–3.

31. Benjamin J. Sadock,.,Virginia A.sadock, Pedro Ruiz,. Kaplan & Sadock's COMPREHENSIVE TEXTBOOK OF PSYCHIATRY. 9 th edition.

32. Hawton K, Casañas i Comabella C, Haw C, Saunders K. Risk factors for suicide in individuals with depression: A systematic review. J Affect Disord. 2013 May 1;147(1):17–28.

33. Behzadifar M, Dehghan H, Saki K, Behzadifar M, Keshavarzi A, Saran M, Sari AA. Evaluation efficacy and safety of Vortioxetine 20 mg/d versus placebo for treatment Major Depressive Disorder: A systematic review and meta-analysis of randomized controlled trials. Pharmacology & Pharmacy. 2015;6:221–231.

34. Defining remission by cut off score on the MADRS: selecting the optimal value. Hawley CJ, Gale TM, Sivakumaran T, Hertfordshire Neuroscience Research group. J Affect Disord. 2002 Nov; 72(2):177-84.

35. Moderate and severe depression. Gradations for the Montgomery-Asberg Depression Rating Scale. Müller MJ, Szegedi A, Wetzel H, Benkert O J Affect Disord. 2000 Nov; 60(2):137-40.

36. A new depression scale designed to be sensitive to change. Montgomery SA, Asberg M Br J Psychiatry. 1979 Apr; 134():382-9.

37. Nasr S J, Altman E G, Robin M, Johe T H, Burg B. Correlation of the Hamilton and Carroll depression rating scales: a replication study among psychiatric outpatients. J CIin Psychiatry 1984:45: 167- 168.

38. Eskelinen M, Korhonen R, Selander T, Ollonen P. Beck depression inventory as a predictor of long-term outcome among patients admitted to the breast cancer diagnosis unit: a 25-year cohort study in Finland. Anticancer Res. 2017;37(2):819–824.

39. Thase ME. Effects of venlafaxine on blood pressure: a meta-analysis of original data from 3744 depressed patients. J Clin Psychiatry. 1998 Oct;59(10):502–8.

40. Sharma. Principles of pharmacology. 3 rd edition.

41. Brunton L, Chabner BA, Knollman B. Goodman & Gillman's The Pharmacological Basis Of Therapeutics With DVD. 12 edition. New York: McGraw Hill Education; 2011. 1808 p.

42. Satoskar RS, Rege NN, Tripathi RK, Bhandarkar SD. Pharmacology and Pharmacotherapeutics. Elsevier; 2017. 1200 p.

43. Montejo-González A, Llorca G, A J, Ledesma A, Bousoño M, Calcedo A, et al. SSRIinduced sexual dysfunction: Fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. J Sex Marital Ther. 1997;23(3):176–94.

44. Uvais NA, Sreeraj VS, Sathish Kumar SV. Sertraline induced mandibular dystonia and bruxism. J Fam Med Prim Care. 2016 Dec;5(4):882–4.

45. Jacob S, Spinler SA. Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults. Ann Pharmacother. 2006 Sep;40(9):1618–22.

46. Covyeou JA, Jackson CW. Hyponatremia Associated with Escitalopram. N Engl J Med. 2007 Jan 4;356(1):94–5.

47. Yasui-Furukori N, Hashimoto K, Tsuchimine S, Tomita T, Sugawara N, Ishioka M, et al. Characteristics of Escitalopram Discontinuation Syndrome: A Preliminary Study. Clin Neuropharmacol. 2016 Jun;39(3):125–7.

48. Ceskova E, Silhan P. Novel treatment options in depression and psychosis. Neuropsychiatr Dis Treat. 2018 Mar;Volume 14:741–7.

49. Zhang MW, Ho R. Critical appraisal of existing ketamine trials: existing limitations and limited applicability of treatment. Am J Psychiatry. 2016;173:431.

50. Xu Y, Hackett M, Carter G, et al. Effect of low-dose and very low-dose ketamine among patients with major depression: a systematic review and meta-analysis. Int J Neuropsychopharmacol. 2016;19:1–15.

51. Garay RP, Zarate CA Jr, Charpeaud T, et al. Investigational drugs in recent clinical trials for treatment-resistant depression. Expert Rev Neurother. 2017;29:1–17.

52. Fava M, Memisoglu A, Thase ME, et al. Opioid modulation with buprenorphine/samidorphan as adjunctive treatment for inadequate response to antidepressants: a randomized double-blind placebo-controlled trial. Am J Psychiatry. 2016;173:499–508.

53. Rucker JJ, Jelen LA, Flynn S, Frowde KD, Young AH. Psychedelics in the treatment of unipolar mood disorders: a systematic review. J Psychopharmacol. 2016;30:1220–1229.

54. Nichols DE, Johnson MW, Nichols CD. Psychedelics as medicines: an emerging new paradigm. Clin Pharmacol Ther. 2017;101:209–219.

55. Ellul P, Boyer L, Groc L, Leboyer M, Fond G. Interleukin-1beta-targeted treatment strategies in inflammatory depression: toward personalized care. Acta Psych Scand. 2016;134:469–484.

56. Sarris J, Murphy J, Mischoulon D, et al. Adjunctive nutraceuticals for depression: a systematic review and meta-analyses. Am J Psychiatry. 2016;173:575–587.

57. Jones LL, McDonald DA, Borum PR. Acylcarnitines: Role in brain. Prog Lipid Res. 2010 Jan;49(1):61–75.

58. Wang S-M, Han C, Lee S-J, Patkar AA, Masand PS, Pae C-U. A review of current evidence for acetyl-l-carnitine in the treatment of depression. J Psychiatr Res. 2014 Jun;53:30–7.

59. Kido Y, Tamai I, Ohnari A, Sai Y, Kagami T, Nezu J, et al. Functional relevance of carnitine transporter OCTN2 to brain distribution of l-carnitine and acetyl-l-carnitine across the blood-brain barrier: Expression of OCTN2 at blood-brain barrier. J Neurochem. 2008 Jul 7;79(5):959–69.

60. Pulvirenti G, Valerio C, Spadaro F, D'Agata V, Freni V, Nardo L, et al. Acetylcarnitine reduces the immobility of rats in a despair test (constrained swim). Behav Neural Biol. 1990 Sep;54(2):110–4.

61. Perera TD, Coplan JD, Lisanby SH, Lipira CM, Arif M, Carpio C, et al. Antidepressant-Induced Neurogenesis in the Hippocampus of Adult Nonhuman Primates. J Neurosci. 2007 May 2;27(18):4894–901.

62. Matrisciano F, Panaccione I, Zusso M, Giusti P, Tatarelli R, Iacovelli L, et al. Group-II metabotropic glutamate receptor ligands as adjunctive drugs in the treatment of depression: a new strategy to shorten the latency of antidepressant medication? Mol Psychiatry. 2007 Aug;12(8):704–6.

63. Cuccurazzu B, Bortolotto V, Valente MM, Ubezio F, Koverech A, Canonico PL, et al. Upregulation of mGlu2 Receptors via NF-κB p65 Acetylation Is Involved in the Proneurogenic and Antidepressant Effects of Acetyl-L-Carnitine. Neuropsychopharmacology. 2013 Oct;38(11):2220–30.

64. Levine J, Kaplan Z, Pettegrew JW, McClure RJ, Gershon S, Buriakovsky I, et al. Effect of intraperitoneal acetyl-L-carnitine (ALCAR) on anxiety-like behaviours in rats. Int J Neuropsychopharmacol. 2005 Mar;8(1):65–74.

65. Foreman PJ, Perez-Polo JR, Angelucci L, Ramacci MT, andTaglialatela G. Effects of acetyl- L-carnitine treatment and stress exposure on the nerve growth factor receptor (p75NGFR) mRNA level in the central nervous system of aged rats. Prog Neuropsychopharmacol Biol Psychiatry 1995; 19: 117-133.

66. Di Cesare Mannelli L, Vivoli E, Salvicchi A, Schiavone N, Koverech A, Messano M, et al. Antidepressant-like effect of artemin in mice: a mechanism for acetyl-l-carnitine activity on depression. Psychopharmacology (Berl). 2011 Nov;218(2):347–56.

67. Peet M, Murphy B, Shay J, andHorrobin D. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. Biol Psychiatry 1998; 43: 315-319.

68. Olusi SO, andFido AA. Serum lipid concentrations in patients with major depressive disorder. Biol Psychiatry 1996; 40: 1128-1131.

69. Nakamura J, Koh N, Sakakibara F, Hamada Y, Hara T, Sasaki H, Chaya S, Komori T, Nakashima E, Naruse K, Kato K, Takeuchi N, Kasuya Y, andHotta N. Polyol pathway hyperactivity is closely related to carnitine deficiency in the pathogenesis of diabetic neuropathy of streptozotocin-diabetic rats. J Pharmacol Exp Ther 1998; 287: 897-902.

70. Pettegrew JW, Levine J, Gershon S, Stanley JA, Servan-Schreiber D, Panchalingam K, andMcClure RJ. 31P-MRS study of acetyl-L-

carnitine treatment in geriatric depression: preliminary results. Bipolar Disord 2002; 4: 61-66.

71. Smeland OB, Meisingset TW, Borges K, Sonnewald U. Chronic acetyl-l-carnitine alters brain energy metabolism and increases noradrenaline and serotonin content in healthy mice. Neurochem Int. 2012 Jul;61(1):100–7.

72. Tolu P. Effects of Long-term Acetyl-L-carnitine Administration in Rats I. Increased Dopamine Output in Mesocorticolimbic Areas and Protection toward Acute Stress Exposure. Neuropsychopharmacology. 2002 Sep;27(3):410–20.

73. Rebouche CJ, Seim H. Carnitine metabolism and its regulation in microorganisms and mammals. Annu Rev Nutr. 1998;18:39-61. doi:10.1146/annurev.nutr.18.1.39.

74. Bersani G, Meco G, Denaro A, Liberati D, Colletti C, Nicolai R, et al. l-Acetylcarnitine in dysthymic disorder in elderly patients: A double-blind, multicenter, controlled randomized study vs. fluoxetine. Eur Neuropsychopharmacol. 2013 Oct 1;23(10):1219–25.

75. Egede L. Major depression in individuals with chronic medical disorders: Prevalence, correlates and association with health resource utilization, lost productivity and functional disability. Gen Hosp Psychiatry. 2007 Sep 1;29:409–16.

76. Fulgente, T., Onori, M., Del Re, M.L., Ferracci, F., Bazzano, S., Ghilardi, M.F., Malatesta, G., 1990. Laevo-acetylcarnitine treatment of senile depression. Clin. Trials J. 27, 155– 163.

77. Nasca, Carla & Bigio, Benedetta & Lee, Francis & Young, Sarah & Kautz, Marin & Albright, Ashly & Beasley, James & Millington, David & Mathé, Aleksander & Kocsis, James & Murrough, James & McEwen, Bruce & Rasgon, Natalie. (2018). Acetyl-L-carnitine deficiency in patients with major depressive disorder. Proceedings of the National Academy of Sciences. 115. 201801609. 10.1073/pnas.1801609115.

ANNEXURE 1- ETHICS CERTIFICATE

GOVT. KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Protocol ID. No.187/2019 Meeting held on 09/04/2019

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval " A COMPARATIVE STUDY OF EFFICACY AND SAFTETY PROFILE OF ACETYL-I-CARNITINE AS AN ADD-ON THERAPY IN TREATMENT OF DEPRESSION AT KILPAUK MEDICAL COLLEGE" submitted by Dr.M. Nilofer Noorie, M.D. Post Graduate, Department of Pharmacology, Government Kilpauk Medical College, Chennai-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

14.5.2019.
DEAN
Govt. Kilpauk Medical College,
Chennai-10.

10/5/19

ANNEXURE -2

Plagiarism Certificate

URKUND

Document Information

Analyzed document	Nilofer noorie thesis.docx (D82259342)
Submitted	10/21/2020 8:09:00 AM
Submitted by	Nilofer Noorie.M
Submitter email	nilofer.m.noorie@gmail.com
Similarity	17%
Analysis address	nilofer.m.noorie.mgrmu@analysis.urkund.com

Sources included in the report

SA	**Tamil Nadu Dr. M.G.R. Medical University / A prospective randomised open label comparative study of efficacy and safety of Es ...** Document A prospective randomised open label comparative study of efficacy and safety of Es ... (D31200436) Submitted by: sharmivj02@gmail.com Receiver: sharmivj02.mgrmu@analysis.urkund.com	53
W	URL: https://quizlet.com/26746852/depression-antidepressants-and-benzodiazepines-flash- ... Fetched: 10/21/2020 8:11:00 AM	2
SA	**Tamil Nadu Dr. M.G.R. Medical University / Sharmi dissertation.docx** Document Sharmi dissertation.docx (D31095601) Submitted by: sharmivj02@gmail.com Receiver: sharmivj02.mgrmu@analysis.urkund.com	2
W	URL: https://www.researchgate.net/publication/260215282_A_review_of_current_evidence_fo ... Fetched: 10/21/2020 8:11:00 AM	13
SA	**Dopamine Agonists As Antidepressants_A Systematic Literature Study_Kaarel Pullerit ...** Document Dopamine Agonists As Antidepressants_A Systematic Literature Study_Kaarel Pullerit ... (D61511354)	2
W	URL: https://www.researchgate.net/publication/221837270_Emerging_drugs_for_major_depres ... Fetched: 2/19/2020 4:51:06 PM	1
W	URL: https://www.researchgate.net/publication/12203290_Acetyl-L-carnitine_physical-chem ... Fetched: 10/21/2020 8:11:00 AM	4

ANNEXURE – 3

CASE REPORT FORM

Name: Address:

Age:

Sex: Phone No:

Op No: Date:

Presenting complaints:

Past history:

Hypothyroidism	Yes/No
Diabetes Mellitus	Yes/No
Systemic Hypertension	Yes/No
Seizure Disorder	Yes/No
Renal Failure	Yes/No
Chemotherapy/Drug intake	Yes/No

Family History:

Menstrual History:

LMP- / /2019,Preg Score - P L A ,Lactation Y*es/N*

Personal history:

Alcoholic - *Yes/No,* Quantity- ml/Day, Duration –

Smoker - *Yes/No,* Quantity- ml/Day, Duration –

Physical examination:

Height -____cm, Weight- ____cm, BMI-_____.

Pallor/Icterus/Cyanosis/Clubbing/LymphNode/Pedal Edema.

CVS –

RS—

P/A—

CNS –

MENTAL STATUS EXAMINATION –

DIAGNOSIS–

Melancholic features *Yes/No*

Psychotic features *Yes/No*

INVESTIGATIONS-

INVESTIGATIONS	Date	Date	Date
Complete blood count			
Lipid profile			
Random blood sugar			
Serum creatinine			
Serum urea			
TSH			

Treatment details –

Psychotherapy given : *Yes/No*

Co- morbid psychiatric conditions :

Medications used & dose:

FOLLOW UP FORM

Name: Address:

Age:

Sex: Phone No:

Op No: Date:

Diagnosis :

Montogomery&Asberg Depression Rating Scale (MADRS) Score :

Co-morbid Psychiatric conditions:

Alcohol dependence (during the study period) : *Yes/No*

Smoking (during the study period) : *Yes/No*

Treatment Details

Psychotherapy given : *Yes/No*

Medications used &dose :

ANNEXURE - 4

Montgomery-Asberg Depression Scale (MADRS)

Instructions: The ratings should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5). It is important to remember that it is only rare occasions that a depressed patient is encountered who cannot be rated on the items in the scale. If definite answers cannot be elicited from the patients, all relevant clues as well as information from other sources should be used as a basis for the rating in line with customary clinical practice. This scale may be used for any time interval between ratings, be it weekly or otherwise, but this must be recorded.

1. ***Apparent Sadness***

Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate on depth and inability to brighten up.

0 No sadness
1
2 Looks dispirited but does brighten up without difficulty.
3
4 Appears sad and unhappy most of the time.
5
6 Looks miserable all the time. Extremely despondent.

2. ***Reported Sadness***

Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or feeling of being beyond help without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

0 Occasional sadness in keeping with the circumstances.
1
2 Sad or low but brightens up without difficulty.
3
4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
5
6 Continuous or unvarying sadness, misery or despondency.

3. ***Inner Tension***

Representing feelings of ill-defined discomfort, edginess, inner turmoil mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 Placid. Only reflecting inner tension.
1
2 Occasional feelings of edginess and ill-defined discomfort.
3
4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
5
6 Unrelenting dread or anguish. Overwhelming panic.

4. ***Reduced Sleep***

Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

0 Sleeps as usual.
1
2 Slight difficulty dropping off to sleep or slightly reduced light or fitful sleep.
3
4 Sleep reduced or broken by at least two hours.
5
6 Less than two or three hours sleep.

5. ***Reduced Appetite***

Representing the feeling of loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

0 Normal or increased appetite.
1
2 Slightly reduced appetite.
3
4 No appetite. Food is tasteless.
5
6 Needs persuasion to eat.

6. ***Concentration Difficulties***

Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

0 No difficulties in concentrating.
1
2 Occasional difficulties in collecting one's thoughts.
3
4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
5
6 Unable to read or converse without great initiative.

7. ***Lassitude***

Representing a difficulty getting started or slowness initiating and performing everyday activities.

0 Hardly no difficulty in getting started. No sluggishness.
1
2 Difficulties in starting activities.
3
4 Difficulties in starting simple routine activities which are carried out with effort.
5
6 Complete lassitude. Unable to do anything without help.

8. ***Inability to Feel***

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

0 Normal interest in the surroundings and in other people.
1
2 Reduced ability to enjoy usual interest.
3
4 Loss of interest in surroundings. Loss of feelings for friends and acquaintances.
5
6 The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. ***Pessimistic Thoughts***

Representing thoughts of guilt. Inferiority, self-reproach, sinfulness, remorse and ruin.

0 No pessimistic thoughts.
1
2 Fluctuating ideas of failure, self-reproach or self-depreciation.
3
4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
5
6 Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable.

10. ***Suicidal Thoughts***

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and the preparations for suicide. Suicidal attempts should not in themselves influence the rating.

0 Enjoys life or takes it as it comes.
1
2 Weary of life. Only fleeting suicidal thoughts.
3
4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5
6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

Total Score:_____

ANNEXURE 5

PATIENT CONSENT FORM IN ENGLISH

Study detail: A Comparative study of efficacy and safety profile of Acety-L-carnitine

add-on therapy in treatment of depression

Study centre: Kilpauk Medical College,Chennai-10.

Patient's Name/age/sex:

Identification Number:

I confirm that I have understood the purpose and procedure of the above study. I have the opportunity to ask questions and all my questions and doubts have been answered to my complete satisfaction.

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.

I understand that the ethics committee and the regulatory authorities will not need my permission to look at my health records, both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However I understand that my identity would not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from the study.

I hereby consent to participate in this study.

As part of this study I agree to reply for the questionnaire as part of diagnosis and treatment assessment.

I have been explained about tablet Acetyl L carnitine 500 mg, two times a day and its efficacy and side effects like rare gastro intestinal symptoms. I agreed to take the tablet for three months.

Patient's Name & Address:

Place with date: Signature/Thumb Impressionof the Patient

Name of the Investigator:

Signature of the Investigator:

ANNEXURE 6

PARTICIPANTS INFORMATION SHEET IN ENGLISH

Investigator:

Name of the participant:

Study Title: A Comparative study of efficacy and safety profile of Acety-L-carnitine add-on therapy in treatment of depression

Purpose of this study:

Depression is a clinical diagnosis. Detailed history, mental status and clinical examination will be done by the Psychiatrist. Therapy will be started by the Psychiatrist according to the severity of the illness. The treatment options available for this disease are SSRI/TCA drugs with addition to symptomatic treatment for patients.Since available oral drugs for the treatment options are few, with many adverse effects and minimal latency period is 2 weeks. Studies are needed to add new oral drugs to minimize the side effects and decrease the latency period .Hence this study will help in adding oral drugs as treatment method for Depression.

Description of the study procedure:

This study will be conducted over approximately 12 week*s*. The routine standard treatment of depression will be decided by the Psychiatrist according to the severity of the illness and symptomatic treatment will be added according to the patient complaints. In this study, after conforming diagnosis of Depressionby clinical examination and classification, participants are put into two groups. One group will be treated with Standard treatment decided by the Psychiatrist (for 3 months) and the other group will receive Tablet Acetyl L Carnitine 500 mg (Three times a day for 3 months) along with standard treatment. The severity of disease will be assessed by Psychiatrist using Montogomery&Asberg Depression Rating Scale(MADRS) . The

results will be compared to see whether Acetyl L Carnitine is beneficial in the treatment of Depression.Participants will not be paid for their involvement in this study.

Discomfort and Risks:

The risk for this study includes rare adverse effects of Acetyl L Carnitine. Acetyl L carnitine is safe and without incidence of significant side effects even with long term administration(1 year).

The most common adverse effects are agitation, Nausea and vomiting.If you suffer any adverse effects due to acetyl L Carnitine, you should contact the study team as soon as possible.

Confidentiality:

Patients who participate in this study and their details will be maintained confidentially and at any cost, those details will not be let-in any publication, information will be provided in such a way that you cannot be identified.

Right to withdraw:

Patients will not be forced to participate or complete the study. Patients can withdraw from the study at any time. At any cost in such circumstances the treatment will not be compromised.

Patient's Name:

Place with date:

Signature/Thumb Impression

of the Patient

Signature of the Investigator: Name of the

Investigator:

ANNEXURE 7

நோயாளிக்கான சுய ஒப்புதல் படிவம்

ஆய்வு விவரம் : மன அழுத்த (Depression) நோய்க்கான சிகிச்சையில்
அசிடில்எல்-கார்னிடைன் (Acetyl L-Carnitine) என்ற மருந்தின் பங்கு

ஆய்வு மையம் : கிழ்பாக்கம் மருத்துவக் கல்லூரி, சென்னை- 10.

நோயாளியின் பெயர் / வயது / பாலினம்:

நோயாளியின் அடையாள எண்:

நோயாளியின் பெயர் மற்றும் முகவரி

தேதி / இடம்:

நோயாளியின் கையொப்பம் , கட்டைவிரல்தாக்கம்

ஆராய்ச்சியாளரின்கையொப்பம்:

ஆராய்ச்சியாளரின் பெயர்:

ANNEXURE 8

பங்கேற்பாளர்கள்தகவல் படிவம்

ஆராய்ச்சியாளர் பெயர்:

பங்கேற்பாளரின் பெயர்:

ஆய்வுப் பெயர் : மன அழுத்த நோய்க்கான(Depression) சிகிச்சையில் அசிடில்எல்-கார்னிடைன்(Acetyl L-Carnitine)என்ற மருந்தின் பங்கு

இந்தஆய்வின்நோக்கம்:

மன அழுத்தம் என்பது ஒரு நாள்பட்டநோயாகும். இது மருத்துவப் பரிசோதனை (ம) கேள்வித்தாள் மதிப்பீடு மூலம் கண்டறியப்படுகிறது.இந்தநோய்க்கான சிகிச்சை முறையில் பல வாய்வழி மருந்துகள் இருப்பினும், அவை பல எதிர்மறைவிளைவுகள்ஏற்படுத்தக்கூடியவையாக இருப்பதால், புதிய வாய்வழி மருந்துகளை சேர்க்க ஆய்வுகள் தேவைப்படுகின்றன. எனவே இந்த ஆய்வு மன அழுத்தநோய்க்கான சிகிச்சை முறையில் புதிய வாய்வழி மருந்துகளை சேர்க்க உதவும்

ஆய்வு நடைமுறை விவரம்:

இந்த ஆய்வு 12 வாரங்கள் நடத்தப்படும். இந்த ஆய்வில் பங்கு பெற விரும்பும் மனஅழுத்தநோய் உடையவர்களுக்கு இரத்த பரிசோதனை (ம) கேள்வித்தாள் மதிப்பீடு செய்தபிறகு இரு குழுக்களாக பிரிக்கப்படுகின்றனர். ஒரு குழுவில் உள்ள நோயாளிகளுக்குவழக்கமான மருந்துகள்கொடுக்கப்படும். மற்றொரு குழுவில் உள்ள நோயாளிகளுக்கு மேற்கண்ட சிகிச்சை முறையுடன் அசிடில்-எல்-கார்னிடைன் மாத்திரை 500 மி.கி. (நாளொன்றுக்கு 2 மாத்திரைகள்வீதம் 2 வேளைகளில்)கொடுக்கப்படும். சிகிச்சைக்கு முன்பும், சிகிச்சைக்குப் பின்பும் நோய்களின்தீவிரம், தன்மையில் ஏற்படும் மாற்றத்தை, வினா-விடைகள (சுமார் 10-15 நிமிடம்எடுக்கும்) மூலம் மதிப்பீடு செய்யப்படும். அசிடில்-எல்-கார்னிடைன் மன அழுத்தத்தில் சிகிச்சையளிப்பதில் நன்மை அடைகிறதாஎன்பதைப் பார்க்க இரு குழுக்களின் முடிவுகள் ஒப்பிடப்படும்.

ஆய்வின்காலத்திற்கு முன்பும் பின்பும் அனைத்துபங்கேற்பாளர்களுக்கும் வழக்கமான ரத்த பரிசோதனை மேற்கொள்ளப்படும். பங்கேற்பாளர்கள் தங்கள் ஈடுபாட்டிற்கு பணம் ஏதும் செலுத்தப்பட மாட்டார்கள்.

அசௌகரியம் மற்றும் அபாயங்கள்:

இந்தஆய்விற்கானஆபத்து அசிடைல் எல் கார்னிடைனின்அரிதான பாதகமானவிளைவுகள் ஆகும். அசிடைல் எல் கார்னைடைன் பாதுகாப்பானது மற்றும் நீண்டகாலம் உட்கொள்ளும் போதும் (1 வருடம்) கூட குறிப்பிடத்தக்க பக்க விளைவுகள் ஏற்படாது என ஆய்வுகள் தெரிவிக்கின்றன.

மிகவும் பொதுவான பாதகமானவிளைவுகள்குமட்டல் மற்றும் வாந்தி, குடல் சம்மந்தமானஉபாதைகள்ஆகியவை ஆகும்.அசிடைல் எல் கார்னிடைன் காரணமாக நீங்கள் எந்தவொரு எதிர்மறையான விளைவுகளையும் சந்தித்தால், நீங்கள் உடனடியாக ஆய்வுக் குழுவைத்தொடர்பு கொள்ள வேண்டும்.

இரகசியத்தன்மை:

இந்த ஆய்வில்பங்கேற்கிற நோயாளிகள் மற்றம் அவர்களின் விவரங்கள் இரகசியமாக பராமரிக்கப்படும்.

ஆய்விலிருந்து வெளியேறும் உரிமை:

நோயாளிகள் ஆய்வில் பங்கேற்க அல்லது ஆய்வு முடிக்க நிர்பந்திக்கப்பட மாட்டார்கள். எந்தநேரத்திலும் நோயாளிகளுக்கு இந்த ஆய்வில் இருந்து விலக முடியும். இத்தகைய சூழ்நிலைகளில் அவர்களுடைய சிகிச்சையில் எந்த வித சமரசம் செய்யப்படமாட்டது.

நோயாளியின் பெயர்

தேதி / இடம்

நோயாளிகையொப்பம் / கட்டைவிரல்தாக்கம்

ஆராய்ச்சியாளரின்கையொப்பம்:

ஆராய்ச்சியாளரின் பெயர்: