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COMPARATIVE STUDY OF EFFICACY AND SAFETY OF ESCITALOPRAM VERSUS SERTRALINE IN MAJOR DEPRESSIVE DISORDER

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ABSTRACT

Depression is a commonly occuring mental health disorder affecting allsectors of people worldwide. Mental health is equally emphasised as that of physical health. Depression, an exasperating disorder shows alarming hike in the present and recent past. Selective serotonin reuptake inhibitors are first choice of drugs for depression and frequently prescribed. Still it has not been possible to declare one particular drug to be more efficacious than the other. The purpose of this study is to compare two of the drugs from this class of SSRIs, namely Sertraline and Escitalopram, in terms of efficacy and safety among major depressive disorder patients.

Methodology:

After approval from Institutional Ethical Committee, 120 patients wererecruited and randomised into either group A to receive Tab.Escitalopram 10-20mg/day or group B to receive Tab.Sertraline 50-200mg/day.Demographic details and complete history were recorded during enrolment. Clinical examination, screening with Hamilton depression rating scale and labinvestigations were done at baseline.

Efficacy was measured by response in terms of improvement of symptoms assessed by scoring with Hamilton Depression Rating Scale at baseline, at 4, 8, and 12 weeks. **Safety** wasensured by recording vitals of the patients and laboratory parameters atbaseline, 4, 8, 12 weeks of study period. Safety was assessed by recording adverse drug reactions reported voluntarily or observed clinically or changes reported in lab investigation during follow up.

Results:

Mean HAM-D score reduction from 20.77 to 8.75 in group A (Escitalopram) and 20.96 at baseline to 8.65 in group B (Sertraline) after12 weeks therapy was statistically significant within groups. Response rate assessed by reduction of mean HAM-D score did not show statistically significant difference between two groups. The occurrence of adverse effects in sertraline group was higher than escitalopram group and this difference wasfound to be statistically significant (P=0.007).The study confirms that both Escitalopram and Sertraline are appropriate as first line drugs in treatment for depression. Both drugs showed equal efficacy in producing response and remission. Escitalopram was better tolerated with less number of reported adverse events than sertraline.

Key Words: Depression, Escitalopram, Sertraline, Hamilton Depression Rating Scale

INTRODUCTION

Depression is a common mental health disorder affecting all sectors ofpeople worldwide. WHO defines Health as " a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"[1]. So Mental health needs to be equally emphasized as physical health. Depression, which increases suicide risk is an exasperating disorder with an alarming hike in the present and recent past.

Depressive disorder is a broad term encompassing major depressive disorder (MDD) (including major depressive episode), persistent depressive disorder (dysthymia), disruptive mood dysregulation disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified and unspecified depressive disorder[2]. Of these major depressive disorder (MDD) and persistent depressive disorder comprise major sub categories.

All forms of depressive disorders share common symptoms of mood changes i.e, irritable, sad and empty along with cognitive and somatic features which can cause significant impact on the individual's functional capability and capacity. The distinguishing part in the above spectrum of depressive disorders is the time of occurrence, duration of symptoms or episodes, and the diagnosed etiology[2].

All forms of depressive disorders share common symptoms of mood Selective serotonin reuptake inhibitors are first choice of drugs for depression and are frequently prescribed. Still it has not been possible to declare one particular drug in this class to be more efficacious than the other[5]. The purpose of this study is to compare two of the drugs from this class of SSRIs, namely Sertraline and Escitalopram, in terms of efficacy and safety among major depressive disorder patients, attending psychiatric outpatient department in MAHESHWARA MEDICAL COLLEGE
Prevalence of depressive disorders has been estimated to show increasing trend, and more studies are done to explore the risk factors, etiology, epidemiology, genetic role, neuro anatomical contributions, biochemical markers, theories of neurotransmission, drugs and diseases commonly associated with depression, current guidelines for managing major depressive disorder, pharmacological and non pharmacological modalities of management, percentage of response to those modalities and safety of variousinterventions.

Though multiple classes of drugs are available for pharmacological management of depression with evidence of reversing prefrontal cortical and hippocampal atrophy seen in depressed patients, SSRIs are the main stay of treatment for MDD[3]. When the preferred outcome is complete symptom remission, still there is significant group of MDD patients (50%) who are poor responders to drug treatment[3]. Recent studies confirm the fact ,that even with initial or successive treatment ventures, significant proportion of patients do not continue to show adequate therapeutic response. Clinical response mostly tends to fall short of full symptom remission. Depressive disorders turn difficult to treat because of its inherent tendency to recur, relapse and remit, added with under dosing and poor patient compliance[4].

Selective serotonin reuptake inhibitors are first choice of drugs for depression and are frequently prescribed. Still it has not been possible to declare one particular drug in this class to be more efficacious than the other[5]. The purpose of this study is to compare two of the drugs from this class of SSRIs, namely Sertraline and Escitalopram, in terms of efficacy and safety among major depressive disorder patients, attending psychiatric outpatient IN MAHESHWARA MEDICAL COLLEGE

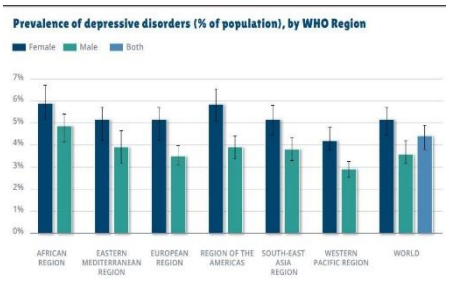


Figure - 1Shows sex related differences in prevalence of depression inWHO regions.

Marital status of an individual significantly influence the development of depression. Single ie, divorced and widowed individuals show increased prevalence. However, prevalence of depression based on marital status did notshow any sex differences[20].

Socio-economic status and depression : People belonging to Lower socio economic class show higher prevalence of depression than among people from higher socioeconomic class. Prevalence rises with decreasing socio economic status[20].

Maternal health and depression : Women diagnosed with major depressive disorder during their antenatal period take poor care of themselves, many engage in alcohol and drug abuse that is detrimental to the fetus. All these culminate in decreased or abnormal development in the fetus, increases complications like pre eclampsia during the pregnancy and delivery, leadingto low birth weight, malnourished and chronically ill babies. Perinatal depression also affects language, social and cognitive development of the offspring. Even after adjusting the confounding factors of socio economic status and others, mothers with perinatal depression have five times more risk of producing infants with stunted growth which become evident by 6 months of age[9]. Children born to mothers with depression have 5 times more risk of developing depression by 16 years of age than the adolescents born to non depressed mothers[25]. Role of hormonal changes involving progesterone, estrogen, TSH that is drastic during pregnancy and nutritional influence on development of depression requires further evidence[25]. Depression is found to be significantly high among women during perinatal period and incidence of depression during postnatal period is estimated to be 11%[12]. To sum up the epidemiological prevalence, depression shows higher incidence among women, older age groups, poor socio economic background,among persons with declined nutritional status, in single, divorced or widowed, in unemployed, and those living in urban areas and nuclear familiesthan in joint families[12].

Genetic risk factors for depression

Family based studies and twin studies show strong genetic influence ondevelopment of depression as evidenced by recurrent illness and young age onset. Unexpected discontinuation or loss of pregnancy is identified as significantly major single risk factor leading to depression[26].Drugs causing depression

- Cancer chemotherapy is a long course with many side effects and by itself can lead to 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 too have a role as a cause of depression.
- Anti hypertensive drug, methyl dopa often used for treating PIH in pregnant women is also implicated in causing depression.
- Other drugs that can produce depression includes are anti-parkinsoniandrugs like amantadine, levodopa and bromocriptine. anti-psychoticslike 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 cause depression.
- NSAIDS, antihistaminics like ranitidine, and cholinergic drugphysostigmine, are known to cause depression[27].
- Hormonal agents like oral contraceptive pills and tamoxifen can cause depression. Prednisolone and Reserpine simulate endocrine andneurochemical changes similar to the changes observed in endogenousMajor Depressive Disorder. Prednisolone causes hypercortisolism,while reserpine deplete mono amine transmitters which in turn precipitates a Major Ddepressive Episode in vulnerable population [26]

SCALES FOR ASSESSMENT OF SEVERITY OF DEPRESSION

Various standard recommended scales that are available currently forassessment of severity of depression includes :

1) HAM-D (Hamilton Depression rating scale)(HAM-D17, HAM-D21, HAM-D24)
2) MADRS (montgomery-Asberg Depression Rating Scale)
3) CGI scale (Clinical Global Impression)
4) QIDS (The16-item Quick Inventory of DepressiveSymptomatology)
5) IDS (The 30-item Inventory of Depressive Symptomatology)

Advantages of SSRIs over TCAs

SSRIs have better tolerability, acceptability and better safety than first generation tricyclic antidepressants. SSRIs do not produce antihistaminic and anticholinergic side effects, they cause little or no sedation and do not interfere with psychomotor and cognitive functioning. SSRIs do not cause alpha adrenergic blockade and hence postural hypotension does not occur with SSRIs. This makes them drug of choice in elderly patients too. They do not precipitate seizures or produce cardiac arrhythmias even in overdose[43]. In a depressed individual there are less serotonin for neurotransmission and increased number of serotonin presynaptic auto receptors and post synaptic

STUDY DRUG - ESCITALOPRAM

Escitalopram belongs to Selective Serotonin Reuptake Inhibitors (SSRIs) class of anti-depressants. Escitalopram is the S-enantiomer of citalopram . It is twice potent than citalopram. Extensive in vivo and in vitro studies revealed that R-enantiomer is inactive, while S-enantiomer is active and produces the pharmacological effects of citalopram. Among the SSRIs Escitalopram is more selective for serotonin transporters than that of dopamine or norepinephrine .

Figure 2: Citalopram : contains both R and S enantiomers

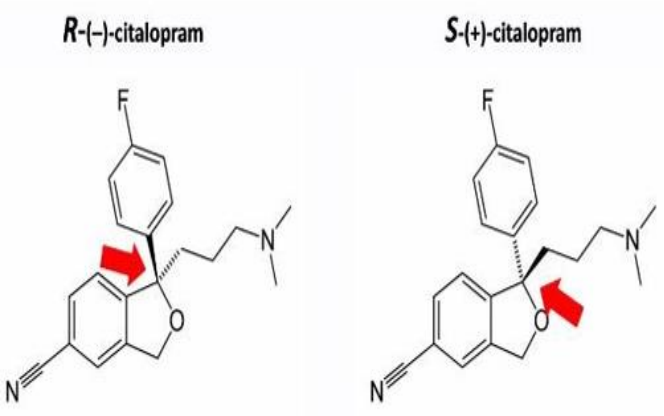
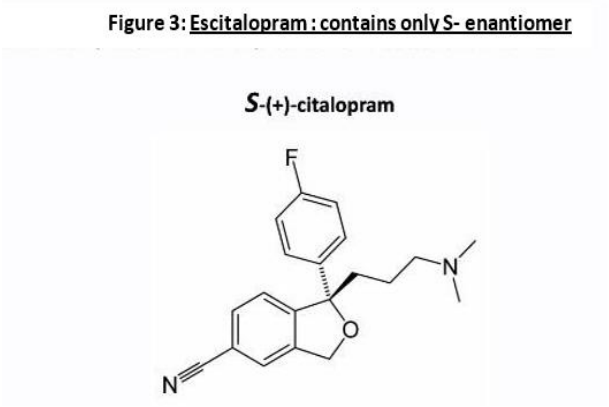


Figure 3: Escitalopram : contains only S- enantiomer



Citalopram is safe and better tolerated and has been used for over 35 million patients after its approval since 1989. Citalopram a racemic mixture of R ,S enantiomers requires higher dose to achieve therapeutic effects, while Escitalopram with pharmacologically active S enantiomer alone produces therapeutic effect at a lower dose. Development of Escitalopram has enabled in halving the dose of the drug used in treatment of depression, preserving therapeutic efficacy. Hence a dose of 10mg was tried successfully in trials for treating depression. This dose is found to be effective and well tolerated for treating major depressive disorder in all levels of healthcare settings[53]. Escitalopram, is an effective first-line option in the management of patients with MDD[54].

Pharmacological actions :

- Escitalopram is a highly selective potent, dose-dependent inhibition of the human serotonin transporter, inhibiting serotonin reuptake into presynaptic nerve terminals resulting in increased serotonergic activity in the CNS.
- Escitalopram causes minimal inhibition of Norepinephrine transporter (NET)
- Escitalopram induces alterations in neurotrophic activity and multiple signaling pathways[41].
- Unlike other SSRIs, escitalopram binds to a primary high-affinity site on the serotonin transporter protein and to a secondary, lower-affinity allosteric site resulting in stable prolonged drug binding. Radioligand binding assays support higher selectivity of escitalopram for the humanserotonin transporter protein, than other SSRIs, including citalopram[55].

Uses Of Escitalopram

- Depression
- Anxiety disorders including panic disorder
- Obsessive compulsive disorder and
- Social anxiety disorder[58].

Adverse Effects: Escitalopram has less adverse drug reactions compared to other SSRIs, highest therapeutic efficacy when compared with citalopram, fluoxetine, generic paroxetine, paroxetine CR, sertraline, venlafaxine and venlafaxine XR[59].

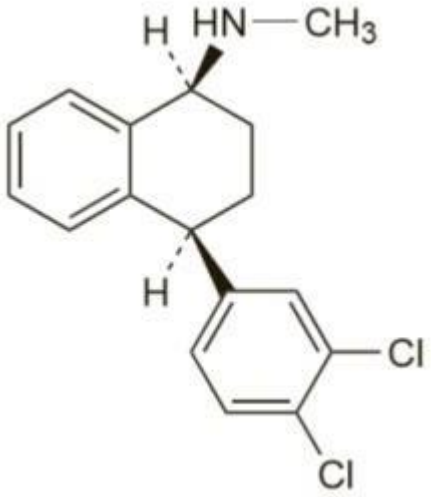
Patients treated with escitalopram had nausea, ejaculation disorder, insomnia, diarrhoea, somnolence, dry mouth and dizziness. A large meta- analysis of data from placebo controlled studies that used escitalopram, revealed that no suicides with the drug occurred within the first 2 weeks or throughout up to 24 weeks of therapy[55]. Higher doses in low clearance states is associated with increased prevalence of ADS. It is found that high steady- state concentration of escitalopram is a risk factor for developing ADS..Tapering of doses over an extended period of time is recommended for all patients to prevent ADS[51]. Though escitalopram has least propensity to causehyponatremia, there are about 8 cases reported till date that are implicating escitalopram as the agent responsible for inducing hyponatremia[60]. Further studies are required to confirm the association of occurrence of

hyponatremia in patients treated with escitalopram.
Escitalopram has a predictable tolerability profile with transient adverse events of mild to moderate severity and a low propensity to produce drug interactions. Sexual dysfunction with escitalopram treatment occurs to a similar or lower extent as compared with paroxetine, to a similar or greater extent as compared with the SNRI duloxetine and bupropion. Escitalopram is well tolerated in treatment for moderate to severe MDD[54].

Drug-drug interactions of Escitalopram
As Escitalopram is metabolized by three cytochrome P450 (CYP) hepatic enzymes in humans, each enzyme offers relatively comparable contributions to intrinsic clearance of the drug in the body. With 3 parallel routes of biotransformation, a drug interaction that interferes with any one of these enzyme isoforms is least likely to affect overall drug clearance rates. Moreover, escitalopram and its 2 metabolites have only weak-to- negligible inhibitory effects on CYP enzymes, hence they are least likely to be producing clinically significant drug interactions mediated through these metabolic pathways. High protein binding nature increases the possibility of displacement of other protein bound drugs. Escitalopram is only 55% bound to human plasma proteins, further reducing its potential for producing drug- drug interactions[61].

ACTIVE CONTROL - SERTRALINE
Sertraline is an anti depressant belonging to the class of SelectiveSerotonin Reuptake Inhibitors (SSRIs). Sertraline (1 S,4S-N-methyl-4-[3,4- dichlorophenyl]- 1,2,3,4-tetrahedro-l-napthylamine) is a naphthylamine derivative with unique antidepressant chemical structure. It exerts its effect by inhibiting reuptake of serotonin into brain synaptosomes, with weak effects on dopamine and norepinephrine reuptake[62] [63].

Figure 4: Chemical structure of Sertraline[64]



Sertraline is an antidepressant and antipanic agent that is a potent and selective inhibitor of serotonin reuptake into the presynaptic terminal. Selective serotonin reuptake inhibitors (SSRIs) depress the firing of neurons in the raphe nucleus, which in turn may affect norepinephrine neurons of the locus coeruleus. Increased firing of locus coeruleus neurons leads to desensitization of the postsynaptic and presynaptic receptors, and it has been demonstrated that sertraline leads to subsensitivity of adrenoceptors in rat brain. This blunted adrenoceptor responsivity of the noradrenergic receptor-coupled adenylate cyclase system occurs after repeated doses of many antidepressants and the same has been evidenced after electroconvulsive therapy also. This effect may also partially account for the effectiveness of sertraline as an antipanic agent, as noradrenergic neurons of the locus coeruleus as well as the serotonergic system have been implicated in anxiety.
Sertraline also exert its antidepressant effects through activation of the cAMP pathway, which in turn

leads to regulation of cAMP-dependent proteinkinase and subsequently to activation of the cAMP response element binding protein (CREB). CREB may mediate its effect by inducing increased expression of neuroprotective neurotrophins such as brain-derived neurotrophic factor which, along with CREB, has been shown to be elevated following chronic antidepressant and electroconvulsive therapy. The effect of increased neurotrophins is to mitigate hippocampal changes associated with exposure to stress. This model of antidepressant action provides the bestcurrent hypothesis regarding the mechanism of action of Sertraline[65].

DEPRESSION - VARIED PRESENTATION:

Major depressive disorder with psychosis has increased risk of suicidality than with depression alone. These patients are treated with combination of anti depressants and antipsychotics. Clomipramine and the selective serotonin reuptake blockers have demonstrated efficacy in the management of obsessive-compulsive symptoms in addition to their antidepressants efficacy[76].

Depression with cognitive dysfunction synonym : pseudo dementia, treatment of depression often reverses the symptoms and signs of cognitive dysfunction. Pseudo demented patients have reduced capacity to process information and exert less effort but report more incapacity than do demented patients. The demented group in more advanced stage, typically neither recognize nor complain of their cognitive failure. It is vital that patients with major depression with cognitive disturbance should not be misdiagnosed and thereby denied the antidepressant medication or ECT. Depression related cognitive dysfunction is a reversible condition that resolves with treatment of the underlying depression.

Depression in elderly is similar to young adults in the "core" features, but differ by a less dysphoric mood, somatic symptoms, poor outcome and increased mortality. Antidepressants are effective yet high rate of adverse effects limits its use in the elderly. SSRIs are acceptable. However, notriptyline has a role in severe depression in the elderly. Electroconvulsive therapy (ECT) is effective in old age depression with rapid response in the severely ill.

Depression in children, with moderate severity can be treated with CBT, IPT and other non pharmacological modalities. SSRIs are first line drugs to treat depression in children and adolescents.

Depression with atypical features include severe anxiety, vegetative symptoms of reserved polarity like increased rather than decreased sleep, appetite, and weight, marked mood reactivity, sensitivity to emotional rejection, phobic symptoms, and a sense of severe fatigue that creates asensation of "leaden paralysis" or extreme heaviness of the arms or legs. There is often overlap between patients with atypical depression and patient with anergic bipolar depression. Tricyclic antidepressants yield response ratesof only 35%-50%. MAO inhibitors response rates of 55%-75% in patients with atypical depression. If it is determined that the patient does not wish to, cannot, or is unlikely to adhere to the dietary and drug precautions associated with MAO inhibitor treatment, the use of an alternative antidepressant is indicated. The results of several studies suggest that SSRIs, MAOIs, and possibly bupropion maybe more effective treatment for Atypical depression. SSRI & Bupropion are preferred drugs for treatment of Atypical Depression[78].

Substance abuse / dependence and Depression : depression and alcoholism often coexist which makes a detailed history of substance use mandatory in patients diagnosed with depression. Major depression with comorbid addiction is more likely to attempt suicide with decreased compliance to therapy. In such cases a program to secure abstinence is regarded as a principle priority in the treatment plan. It is advisable, to detoxify such patient before initiating antidepressant therapy.

Benzodiazepines and other sedative hypnotics carry the potential for abuse or dependence and should be used cautiously except as part of a detoxification regimen. Hepatic dysfunction and hepatic enzyme induction frequently complicate pharmacotherapy of patients with alcoholism and other substance abuse. these conditions require careful monitoring of blood levels.

Seasonal depression : Annual episode of depression occur in some individuals usually at the same time (winter onset) each year. It is characterised by atypical features like hypersomnia and overeating. Seasonal affective disorder is treated either with light therapy alone or in combination with antidepressants.

Management of depression associated with other systemic diseases:

- MAOIs interact with sympathomimetic bronchodilators used in Bronchial Asthma. Other antidepressant like SSRIs, TCAs, etc may be used in such group of patients
- Cardiac conditions like Ventricular Arryhythmia, Subclinical Sinus node dysfunction, Conduction defects, prolong QT intervals or history of recent Ml preclude use of tricyclics. The SSRIs, Bupropion, newer antidepressant and ECT appears to be safer for patients withpreexisting cardiac disease.
- Patients with glaucoma may be treated with antidepressants lacking anticholinerigic activity like Bupropion, SSRIs and Trazodone.
- Antihypertensive agents and TCAs may interact to either intensify or counteract the effect of antihypertensive therapy. TCA may antagonize the therapeutic actions of many antihypertensives like guanethidine, clonidine and alpha methyldopa. Concurrent antihypertensive treatment especially with trazodone or MAOIs will induced symptomatic orthostatic hypotension. Dose dependent elevation in blood pressure with venlafaxine makes this agent less preferable in patients with hypertension[(79)].

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