Efficacy of Sertraline in the Treatment of Major Depressive Disorder Among Adult Population: A Systematic Review

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

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Ethics Statement

There were no animal models used in the entire work which prevents the occurrence of any unethical activities which usually arise due to the use of animal models in scientific researches. Moreover, there were no participation of human subjects as well and hence informed consent is not applicable.

Abstract

With an increasing prevalence of Major Depressive Disorder (MDD) throughout the past few years, it has been crucial to examine the effectiveness of antidepressants in order to treat and manage such conditions. Due to the complex heterogenicity in terms of the pathophysiology of such psychiatric disorders, assessing the clinical effectiveness of available pharmacological interventions is of concern. The aim of the systematic review is to investigate the efficacy of an FDA approved antidepressant, Sertraline in the treatment of MDD in adult population. A literature search of Randomized Control Trials (RCTs) was performed in PubMed based on a pre-specification of eligibility criteria in order to extract studies evaluating and comparing the efficacy of Sertraline in patients with clinically diagnosed MDD either with another antidepressant or placebo. Risk of bias as well as methodological qualities of each individual study was also assessed in order to address the qualities of studies incorporated.

Keywords: Sertraline; efficacy; Major Depressive Disorder; antidepressant; Risk of Bias

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List of Acronyms

MDD	Major Depressive Disorder
SSRI	Selective Serotonin Reuptake Inhibitor
SNRI	Selective Norepinephrine Reuptake Inhibitor
TCA	Tricyclic Antidepressants
RCT	Randomized Control Trials
DSM	Diagnostic Statistic Manual
MAOI	Monoamine Oxidase Inhibitor
FDA	Food and Drug Administration
PICOS	Patient Intervention Comparator Outcome Study
PRISMA	Preferred Reporting Items for Systematic Review and Meta Analysis
CKD	Chronic Kidney Disorder
CHF	Congestive Heart Failure
COPD	Chronic Obstructive Pulmonary Disorder
HAM-D RS	Hamilton Depression Rating Scale
SERT	Serotonin Reuptake Transporter

Chapter 1

Introduction

An exceptionally prevalent and a debilitating psychiatric disorder, Major Depressive Disorder (MDD) is characterized by complex underlying etiopathogenesis, the features of which range from the state of being in a phase of anhedonia, diminished cognitive function, vegetative symptoms such as disruption in the sleep cycle as well as loss of appetite with persistent feelings of guilt, hopelessness, despair and increased suicidal ideation. Such mental conditions have a negative impact on both the patients treated and the physicians due to its complicated multifactorial etiology and convoluted association between various social, psychological and biological factors. Such factors are still lacking several significant explanations resulting in uncertainties as there is a gap that can independently elucidate the pathological theory of its pathogenesis, comprising genetics, neurobiology, and neuroimaging. These mental disorders can pose an obstacle in the daily functioning of an individual accompanied with remarkable costs in quality of life and lost work productivity mostly due to sick leaves, absenteeism, short-term disability, and shortfalls in completion of tasks. It was in the year 2008 that the World Health Organization (WHO) categorized depression as the thirds largest source of illness-related burden and is expected to take up the first rank when it comes to being responsible for economic burden. According to a study by B et al., 2007., it was projected that depression would cost the economy 83.1 billion dollars, out of which 51.5 billion would be related to lost productivity at work. The COVID-19 pandemic worsened the scenario with a sharp rise in depressive and anxiety disorders associated with it. A 28% growth of people experiencing depressive symptoms was observed from the base of approximately 193 million individuals to 246 million. From a global perspective, nearly 5% of the

adults suffer from either minor depressive symptoms or MDD and a greater percentage of women suffering than men. A study conducted in the year 2016 by the Global Burden of Diseases, Injuries, and Risk Factors revealed the fact that 34.1 million of the total years lived with disability was caused by depression, which resulted it to rank as the fifth leading cause of YLD (Krishnan & Nestler, 2008).

Though depression can possibly occur at any age, both the clinical and etiological aspects are affected by the age of initial manifestation. Pediatric depression that occurs during childhood usually affects the preschoolers aged three and below. Clinical data have revealed that earlier age of being diagnosed with depression is usually associated with a worse course of depression, with larger likelihood of recurrence, chronicity, and impairment in functioning. However, there are rare cases of childhood diagnosis of depression and majority of the diagnosis of MDD are among the adolescent, early adulthood and among the older adult population with different factors responsible for its cause. The transition from childhood through adolescence and into becoming an adult, the rate of depression rises (J et al., 2004). The various categories of childhood depressions may include those with true inherited early- onset recurrent depression, children who suffered from serious psychosocial adversity, such as violence, parental dysfunction, criminal activity, and family disruption and keep displaying social maladjustment as well as problematic behavior and are less likely to communicate their feelings, associated with self-destructive play themes and also reduced interest with only 50% of adolescents with a diagnosis of pediatric MDD receive treatment prior to reaching adulthood (Greenberg et al., 2003). A study by Kessler et al. (2012) revealed that as opposed to both adolescents (13-17 years) and older adults (65+ years), adults are twice as likely to be diagnosed with MDD and hence the multifactorial condition is also prevalent among young adults and older adults to a greater degree.

1.1 Pathophysiology

In addition to being a complex and heterogeneous disorder having numerous causes, depressive disorders also exhibit symptoms like guilt and sociality that cannot be simulated in animal models and there have been variety of biological and psychological theories that were developed with the aim to explain the origin of MDD. Though the multifactorial etiology of MDD consists of biological, genetic, environmental, and psychosocial factors; the neuroscience community has embraced the original notion known as the "Monoamine Theory of Depression". It states that abnormalities in monoamine neurotransmitters especially serotonin, norepinephrine, and dopamine have a role in the pathophysiology of depression. The justification of this theory of depression is supported by clinical evidences showing that a significant role is played in monoamine neurotransmission by monoamine oxidase inhibitors (MAOs), tricyclic antidepressants (TCAs) and other commonly used class of antidepressants such as selective serotonin receptor inhibitors (SSRIs), serotonin-norepinephrine receptor inhibitors (SNRIs), dopamine-norepinephrine receptor inhibitors (Li et al., 2021).

Glutamate and glycine, the excitatory neurotransmitters and GABA (Gamma Amino Butyric Acid) serves to performs a significant role contributing to the etiology of depression. In the regions such as the brain, CSF, and plasma, the levels of concentration of GABA have been found to be lower in depressed patients than healthy individuals. Antidepressant activities are exerted by GABA by inhibition of ascending monoamine pathways, in the two noteworthy regions called as the mesolimbic and mesocortical systems. It has been evaluated whether drugs which have the ability to antagonize NMDA receptors have antidepressant properties (Sullivan et al., 2000).

Moreover, biological theories of depression explain biological factors such as change in brain structure, endocrinal imbalances such as imbalances in the thyroid hormones, growth hormones,

high cortisol levels etc., have also been linked in the pathophysiology of mood disorders. Serotonin has the ability to modulate neuroplasticity and its malfunction can lead to pathophysiology of depression. Diminished size and neuronal density and decrease in hippocampal volume presented in MRI tests could be due to serotonergic neuroplasticity modulation among the depressive patients (Lanzenberger et al., 2017). The functional and structural brain imaging studies have revealed that there are more hyper intensities in subcortical regions among depressed individuals and on the other hand less anterior brain metabolism on the left side. Numerous traumatic events and unpleasant childhood memories leads to the development of depression later in life. (Li et al., 2021). A remarkable impact on neuroendocrine and behavioral responses might be due to early exposure to extreme stress, wherein cerebral cortex structure in the brain cn be heavily impacted in later stages of life. Reinforcement behaviors, avoidance and attention issues are some behavioral factors that are explained in various behavioral models of depression (Costello, 1972).

Depression could also arise due to genetic malfunction in serotonergic neurotransmission. The s/s genotype degenerate of a repeat in the gene, the serotonin-linked polymorphic region (5-HTTLPR) coding for the serotonin transporter (SLC6A4) is linked with a decrease in serotonin expression, leading to greater vulnerability to depression (Caspi et al., 2010). Monozygotic twins had a very high concordance risk for having MDD, according to genetic studies (Vos et al., 2017).

1.2 Diagnosis

Among the most typical subtypes of MDD are, prenatal depression, seasonal affective disorder, postpartum depression and atypical depression. Major depressive disorder, often termed as clinical depression, differs from ordinary depression in that it lasts for a minimum of two weeks and manifests as more than just sadness. MDD is diagnosed by physicians after carefully examining the symptoms experienced, duration of symptoms being experienced, past medical history and

mental health history. Primary care practitioners can make use of the Patient Health Questionnaire (PHQ-9) tool which solely focuses on the nine specific diagnostic criteria or factors for clinically diagnosing major depression stated in the Diagnostic Statistic Manual- V (DSM- 5), in the heavily crowded outpatient setting wherein the patient load is high (Gutiérrez-Rojas et al., 2020). In accordance to the DSM-5, an identical feature is shared among all depressive disorders: a physical and cognitive change that has a major impact on the person's ability to function along with a sad, empty, or irritated mood. In general, patients with scores of 5 to 9 had either no signs of depression and patients with scores of 15 or higher generally suffered from serious depression. There is a list of criteria outlined in the DSM-5 tool which are crucial to diagnose depression (Green et al., 2010). Apart from one of the many symptoms, there should be presence of either depressed mood or a lack of interest or pleasure along with a minimum of five (DSM-V) or four (DSM-IV) symptoms among depressed patients for at least two weeks. (Sullivan et al., 2000). There is another 21-item questionnaire known as the Beck Depression Inventory developed first in the year1961 which constitutes questions that are able to assess affective, cognitive and somatic aspects of major depression 11 In order to manage MDD successfully and to fix a set of achievable treatment goals, there should be a scenario wherein the decision-making process is shared between the healthcare provider (HCP) and patient but there are several evidences which show the fact that the depressed mental state of the patients result in their inability to understand make appropriate choices (Beck et al., 1961)

1.3 Antidepressants for Management of MDD

One of the initial successful pharmacological treatments for depression was invented through serendipity and the drug iproniazid was discovered, a MAOI. The MAO enzyme consisting of two isozymes MAOA and MAOB act as a safety valve to oxidatively deaminate and breakdown

biogenic and sympathomimetic amines. Hence drugs belonging to the class of MAOIs prevent the degradation the neurotransmitters making them available in the synapse for generating neurotransmission. TCAs were another class of antidepressants and the drug Imipramine, that functions by blocking the reuptake of serotonin and norepinephrine was approved by FDA in 1959 making it the first drug from the class used for treatment of MDD. However, with the use of MAOIs and TCAs, there evolved numerous harmful adverse events among the patients being treated with these particular classes of drug which led to the discovery of a rather more selective therapeutic class of drugs with reduced side effects profile and better tolerability (Hillhouse & Porter, 2015).

1.4 Sertraline- Discovery and Mechanism of Action

It was in the late 1960s, when evidences suggesting the role of serotonin became available in pathophysiology of depression led Eli Lilly, a pharmaceutical industry to develop drug that would selectively block the Serotonin Reuptake Transporter (SERT) arresting the reabsorption of serotonin back into the pre synaptic neurons thereby enhancing its concentration within the synaptic cleft that results in stimulation of the serotonin receptors in the post synaptic neurons. It was in the year 1974 , when the use of Fluoxtetine was first published and later in December, 1987 it was approved by the FDA and launched to the market with the brand the name Prozac in January 1988 as the very first Selective Serotonin Reuptake Inhibitor (SSRI) (Shaw et al., 1967). It was in the late 1970s when the discovery of Sertraline Sertraline, a potent inhibitor of the SERT was approved by the FDA in 1999 for the treatment of posttraumatic stress disorder, depression, obsessive compulsive disorder, and panic disorder began. Marketed as Zoloft by Pfizer, a team of scientists there synthesized a norepinephrine reuptake inhibitor compound named Tametraline that resulted in stimulant side effects in rats and further modifications and selectivity was imparted by

addition of choline substituents and changing its conformation led to invention of Sertraline (*ACS-Award-Team-Innovation*, n.d.). Other than that, Sertraline inhibits the dopamine transporter as well with dissociation constant ≈ 25 nanomolars, serotonin/dopamine ratio ≈ 86 with clinical and laboratory data suggesting that sertraline at higher doses inhibit dopamine reuptake (Tatsumi et al., 1997). Furthermore, treatment with sertraline had an effect in improving depressed patients' subjective wellbeing and life satisfaction in contrast to treatment with antidepressants such as MAOIs and TCAs exhibiting no direct dopaminergic effect because the dopaminergic system has been linked to motivation and reward processes**.** For instance, one study that compared the effects of sertraline (a SSRI) with nortriptyline (a TCA) in elderly depressive individuals discovered that although both medications showed similar improvements in mood, sertraline produced more significant improvements in quality-of-life categories (Bondareff, 2000). Sertraline was found to tend to provide more improvement in quality-of-life indicators compared to amitriptyline (a TCA), according to a similar trial in depressed adult outpatients (Lydiard et al., 1997). Additionally, the activating properties of Sertraline makes it beneficial for treatment of melancholic depressed patients with low energy or hypersomnia hence usually prescribed at daytime to reduce insomnia (Amitai et al., 2015).

There have been numerous studies evaluating the efficacy of antidepressants as standalone therapy and used in combination with other interventions. Due to the extraordinarily increasing rates of MDD among individuals (Proudman et al., 2021), it has been necessary to carry out researches in this particular arena and hence this systematic review aims to examine and comprehensively appraise the clinical efficacy of Sertraline in the treatment of MDD among adults. The objective of the study is to investigate the efficacy of sertraline as the intervention by comparing it with other antidepressants or placebo and evaluating population of study participants, presence of any chronic

disorders, efficacy outcomes evaluated by several scoring methods specific for measuring depression, adverse events as well as the Jadad Score to assess evidence of quality along with the Risk of Bias Assessment.

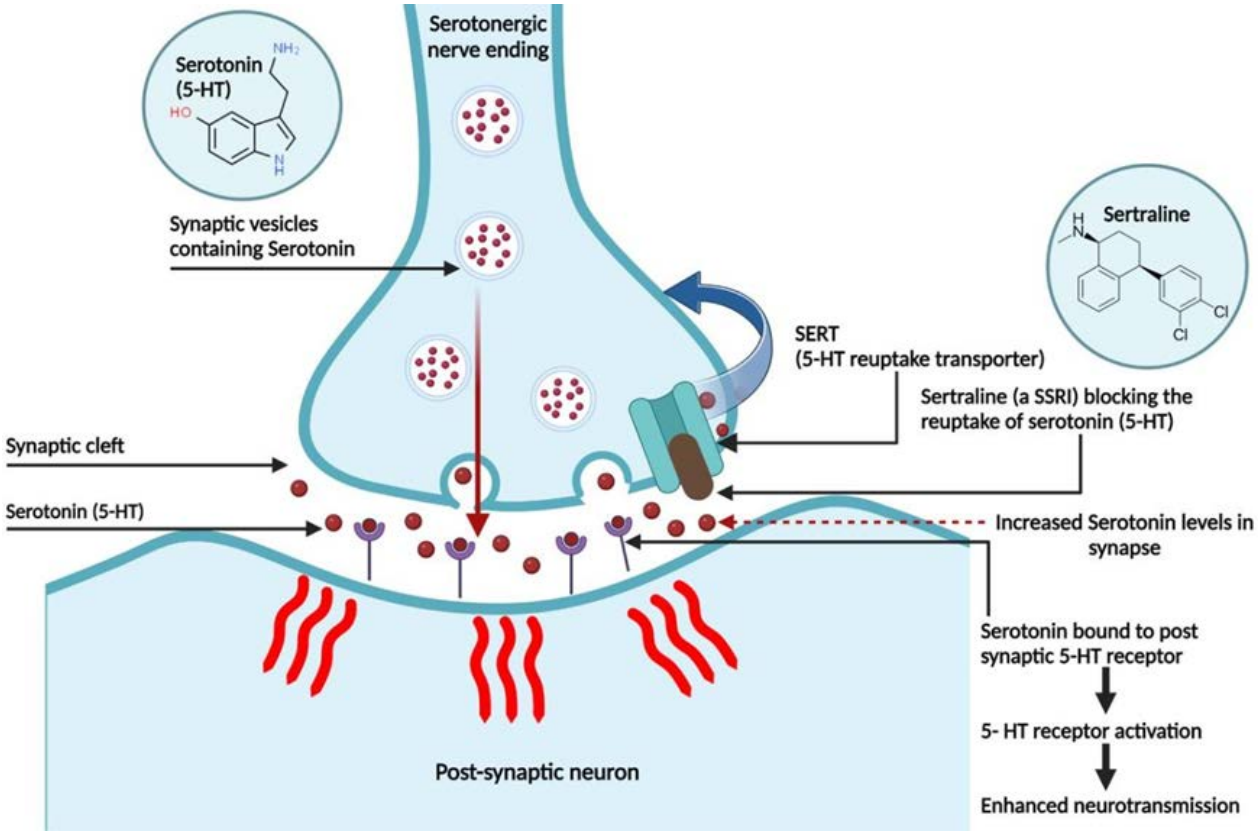

Figure 1: Mechanism of Action of Sertraline. (Figure created using https://www.biorender.com/)

Chapter 2

Methodology

2.1 Data Sources and Search Methods

Relevant and appropriate studies were searched in the PubMed/Medline database published from 2005 till May 2023 that assessed the efficacy of a Sertraline, a Selective Serotonin Reuptake Inhibitor (SSRI) which is an antidepressant administered for the treatment and management of Major Depressive Disorder (MDD) in adults. The search term consisted of some significant keywords, some of which included “Major Depressive Disorder”, “MDD”, “Major Depression”, “Clinical Depression” for the disease, and “Sertraline”, "Zoloft "for the medication. The Boolean operator “OR” was utilized to include synonyms of the terms and the operator “AND” to combine the two sets of terms. In order to retrieve studies that focused on comparing the efficacy of Sertraline in the treatment of MDD, the term “efficacy” was included while search process was carried out. The process of retrieving studies was conducted by applying additional filters and certain criteria which are briefly summarized in the patient, intervention, comparator, outcome, study (PICOS) inclusion and exclusion criteria to build up a refined search process.

2.1.1 Screening Criteria for Study Selection

The systematic review was conducted by screening the literatures that satisfied all the various eligibility criteria which were set using the PICOS inclusion and exclusion strategy and the studies that did not met the requirements were excluded for further analysis. Initially with the help of a developed search string, a broad list of studies were identified from which, a number of articles were filtered and a check for duplicates was run on Rayyans wherein the duplicate articles removed. Furthermore, title and abstracts were screened to extract the most relevant studies

followed by reading out the full texts of the articles carefully in order to eventually select the finalized list of studies to be included. Throughout the rigorous screening process, every selected article was scrutinized in order to reassure whether the pre-specified PICOS inclusion and exclusion criteria were met regarding all the aspects mentioned in

2.2 Inclusion and Exclusion Criteria

2.2.1 Type of Participants

Studies that enrolled adult participants aged 19 and above and those diagnosed with MDD using DSM-IV and DSM-V (Diagnostic and Statistical Manual) criteria or the Beck Depression Inventory-II (BDI-II) were selected for inclusion. Since the safety and efficacy of antidepressant agents in children and older individuals tend to differ from those in the general adult population, the former mentioned population groups were excluded for the review. Moreover, studies that analyzed the efficacy of Sertraline in adult individuals with or without the presence of any existing conditions (apart from MDD) such as Chronic Kidney Disorder (CKD), etc., were also taken into consideration. However, no restrictions were imposed on gender, ethnicity, or any other cultural or demographic factors.

2.2.2 Types of Interventions

The studies were screened such that all the patients underwent treatment with any form of Sertraline after being diagnosed with MDD to be included in the treatment group. The control group on the other hand consisted of treatment procedure with the use of a different class of antidepressant drug, placebo or no treatment.

2.2.3 Type of Study

Randomized Control Trials that were double blinded wherein the efficacy of Sertraline was investigated in the treatment of MDD were incorporated in the study and case-control studies, cohort studies, case series were eliminated.

2.2.4 Type of Outcome Measurements

Since the main aim of the study is to evaluate the clinical effectiveness of Sertraline in treating MDD, primary efficacy outcome is reduction in depression measured by any established scoring system, such as Hamilton Depression Rating Scale (HAM-D RS). Secondary outcomes are measures or data presenting outcomes related to anxiety, health-related quality of life, and reported adverse events.

2.3 Risk of Bias

In order to appraise the Risk of Bias of all of the 13 studies selected for the systematic review, the Cochrane Risk of Bias 2.0 Tool was used. All the five domains in the tool were assessed individually for each study which is described in the results section below in order to generate an overall bias for respective studies.

Table 1: Search Strategy Sample

Number	Search Terms
1.	Sertraline
1.	Zoloft
2.	Efficacy
3.	Depression
4.	Depressive Episode
5.	Depressive Disorder
6.	Randomized
7.	Random
8.	Control
9.	Study
10.	Placebo
11.	Allocation
12.	Treatment
13.	Population

Table 2: Patient Intervention Comparator Outcome Study (PICOS) Inclusion and Exclusion Criteria

Parameter	Inclusion Criteria	Exclusion Criteria
Patient	The adult population aged 19-64which includes the young adults as well as the middle-aged individuals. Along with that, Patients diagnosed with MDD with or without the presence ofany existing disorders.	Children and adolescents were excluded and elderly people aged65 and above were eliminatedfrom the study. Treatment resistant depressedpatients. Patients with severe depression or Suicidal ideation.
Intervention	Sertraline as a mono-therapy	Interventions that combined Sertraline and another antidepressant drug, combination therapy. Studies that evaluated an alternativeand complementary medicine for the treatment of depression (Herbal Preparations) were excluded.
Comparator	Placebo effects or effects of another antidepressant drug belonging to any of the major class of antidepressants.	Combination therapy, exercise, physiotherapy, surgical interventions, etc. were not included.
Study	Double-blinded Randomized Control Trials that were conducted among human participants and published in English language.	Cohort studies, Case control studies, Non-Randomized Cohort studies, Case Series, Retrospective Cohort study, Animal studies, In Vitro research, studies not available in English language.

Chapter 3

Results

3.1 Study Selection

Initially by conducting search in PubMed, 479 studies were identified. By applying additional filters in-built within PubMed database that satisfies some of the selection criteria, 203 studies were extracted. At this point, with the help of Rayyans, a web-based tool 8 duplicate articles were identified and removed, and such a platform has also been useful in screening of abstracts of studies. Furthermore, 195 articles remained to be evaluated based on the screening of abstract and on the inclusion and exclusion criteria developed earlier among which 45 full text articles were assessed thoroughly for eligibility to be included in the systematic review, 32 articles were excluded based on absence of a specific criteria used for diagnosis of MDD (n=7), high patient dropout rates (n=4), patients suffering from psychosis (n=5) and absence of baseline characteristics of patients (n=16). Hence after the rigorous screening procedure, a total of 13 studies were extracted that met the inclusion criteria and were included in the review as shown in Figure 2 below.

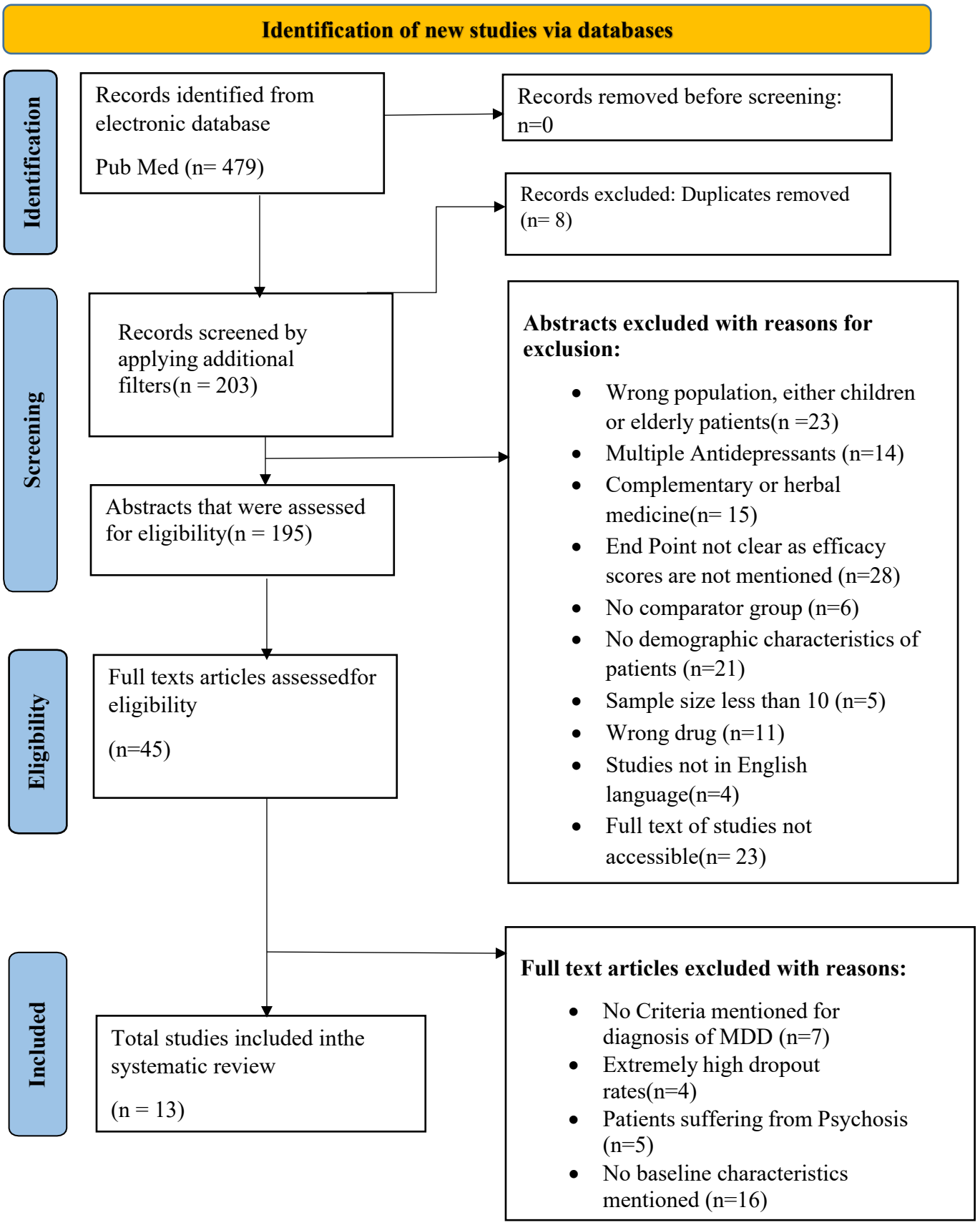

Figure 2: PRISMA Flow Diagram of Selected Studies Included in the Review

3.2 Study Characteristics

3.2.1 Study Design

The 13 studies included were all double-blinded and randomized control trials published between the years 2006 to 2022 and conducted in different regions across the world spanning the Asian, American, and European continent. Although majority of the trials compared the efficacy of Sertraline with Placebo, there were three trials that compared the efficacy of Sertraline with another antidepressant. Mowla et al. (2016) compared the efficacy of Sertraline with an SNRI, Duloxetine, Ch et al. (2022) compared Sertraline with Desvenlafaxine, also an SNRI and Shelton et al. (2006) Compared Sertraline with Venlafaxine XR which also happens to be an SNRI. The studies were conducted in different regions across the world spanning the Asian, North and South American, and European continent. The diagnosis criteria for the studies conducted by Mowla et al. (2016), Hantsoo et al. (2014), O'Connor et al. (2010), Valle-Cabrera et al. (2018), Kamijima et al. (2006), Hedayati et al. (2017), Fann et al. (2017), He et al. (2016), Lustman et al. (2006) and Shelton et al, (2006) were the DSM-IV criteria for diagnosing the presence of MDD among patients. The studies by Friedli et al. (2017) used BDI-II criteria, Greenberg et al. (2020) used the QIDS-SR score and Ch et al. (2022) used DSM-V criteria to diagnose MDD respectively to include patients in the trials.

3.2.2 Patient Criteria

A total of 1901 patients were included in the 13 studies among which 956 patients were assigned to the treatment group; receiving Sertraline and 943 patients belonging to the comparator group either receiving Placebo or any other type of antidepressant; all of them being diagnosed as MDD patients using an appropriate diagnostic tool. Both males and females were recruited in the studies with an exception in the study by Hantsoo et al. (2014) where all the subjects included were

females. Since the study aims to evaluate efficacy of Sertraline among adult population, the participants included were all among the age group 18-64 and studies with participants above or below this range were excluded. Although majority of the studies did not identify the presence or absence of any existing comorbidities among the patients, there were 6 studies that identified patients suffering from an existing condition apart from having MDD. Friedli et al. (2017) identified the subjects suffering from Chronic Kidney Disorder (CKD) undergoing hemodialysis, O'Connor et al. (2010) included patients that suffered from Congestive Heart Failure, Hedayati et al. (2017) included patients with CKD that did not need dialysis, Fann et al. (2017) included Traumatic Brain Injury patients, patients with Chronic Obstructive Pulmonary Disorder were included in the study by He et al. (2016) and lastly patients having type-II Diabetes Mellitus were a part of the study by Lustman et al. (2006).

3.2.3 Drug Doses in Treatment and Comparator Group

Sertraline is available as oral dosage forms (tablet and solution) and are available as 25mg 50mg 100mg, 150mg and usually not given more than 200 mg per day to an adult for depression (nhs.uk, 2022). Majority of the studies used an initial dose of 50mg of Sertraline followed by dose escalation not more than 200mg of Sertraline along with the treatments required among patients suffering from an existing condition mentioned above. The comparator used was Placebo for most of the studies apart from the study by Mowla et al. (2016), which used a mean dose of 55mg of Duloxetine, a dose of 100mg of Desvenlafaxine was used in the study by Ch et al. (2022) and a 225mg/day dose of Venlafaxine XR used in the study by Shelton el al. (2006).

3.2.4 Baseline Severity of Subjects

Baseline characteristics especially the severity of MDD is extremely crucial to assess to evaluate the outcomes of the intervention used in the study. The severity of Depression was assessed using

the HAM-D RS scoring method which is said to be the gold standard for assessing depression as well as in evaluating the efficacy of antidepressants (Bagby et al., 2004). Most of the recruited studies included grade III (moderate), grade IV (severe) and grade V (very severe) depressed patients. The severity of depression in control group was almost like that of the Sertraline group in all studies that had control group as Placebo or any other antidepressant. The details regarding each score of MDD at baseline measured using different scales are enumerated in Table 3.

3.2.5 Endpoint Assessment

The primary efficacy evaluations are based on changes of HAM-D scores measured at baseline and at the end of the study. A 50% or higher reduction in the HAM-D scores after being administered with an antidepressant is usually indicative of clinical efficacy thereby suggesting a positive response to the treatment assigned. A reduction of 25 to 49% in HAM-D scores is said to be indicative of partial response (Asghar et al., 2022). In all the studies included, there was a change in HAM-D rating scale scores observed as reduction in scores when measured at baseline and at the end of study. In the studies by Friedli et al. (2017), Hantsoo et al. (2014), O'Connor et al. (2013), Valle- Cabreraet al. (2018), Kamijima et al. (2006), Fann et al. (2017), He et al. (2016), Ch et al. (2022), Lustman et al. (2006) and Greenberg et al. (2020) there was a statistically significant difference observed in the outcomes of the HAM-D scores between treatment and control group based on the evaluation of p-values of each individual studies. However, in the studies by Shelton et al. (2006), Mowla et al. (2016) and Hedayati et al. (2017), there was no statistical difference observed and all of the above-mentioned outcomes are assessed from the data provided in Table 3.

3.2.6 Adverse Effects

Since Sertraline is an activating SSRI influencing the 5-HT receptors, one of the most common CNS related adverse events noted was insomnia along with headaches and dizziness. Gastrointestinal side effects such as nausea, vomiting as well as diarrhea were mostly present among the sertraline arms. Other noted adverse events include sexual side effects, weight loss, dry mouth etc. among the subjects under Sertraline treatment.

3.3 Risk of Bias Assessment

With the assistance of Cochrane Risk of Bias 2.0 tool, the risk of bias of all the 13 studies were evaluated on five distinct domains such as randomization process, deviations from intended interventions, missing outcome data, measurement of outcome and selection of reported result and were assigned three outcomes “low risk” “high risk” and “some concerns”. By assessing each domain, a finalized overall bias of each study was generated by the algorithm in-built in the tool wherein among the 13 studies included in the review, majority (7 studies) of them showed to have “some concerns” and the rest (5 studies) were a part of “high risk” studies. The risk of bias of the studies are presented in Figure 3 and Figure 4 below.

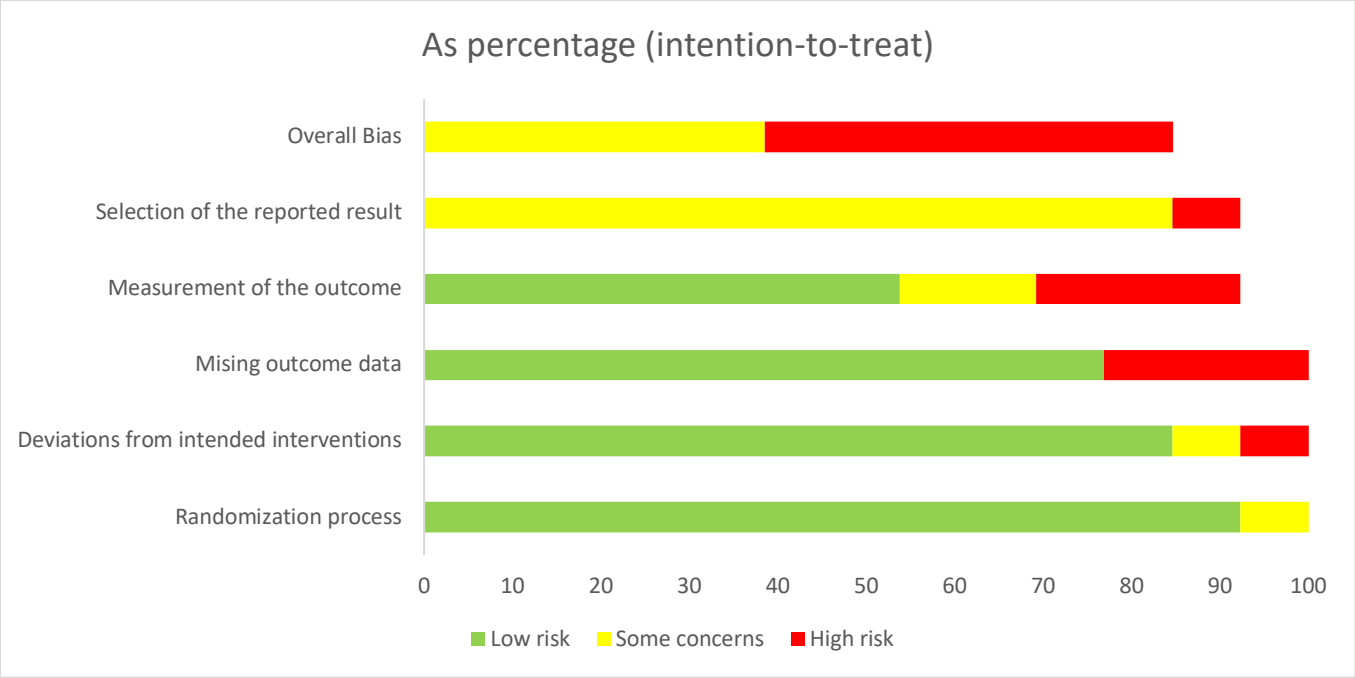

Figure 2: Risk of Bias graph

Figure 3: Overall Risk of Bias of Individual Studies using "Traffic Light Plots"

Table 3: Summaries of Studies Evaluating the Efficacy of Sertraline

Author, Year	**Study type**	**Study details**	**Diagnosis criteria of MDD**	**Pharmacologic alIntervention**		**Treatment regimen**	**Existing comorbid condition**	**Efficacy Outcomes**		**Adverse events**
		1.Origin of study 2. Total subjects, 3.Mean age, 4.Sex, 5.Length of study	***Clinical diagnosisof MDD***	***Treatment Group***	***Control Group***	***Dosage and dose escalation details.***	***Presence of a chronic disorder along with MDD***	***At baseline***	***At the end of the study*** ***p -value***	***Reported serious/mild adverse effects during trial***
Mowla et al., 2016	RCT, Double blinded study	1. Iran 2. 54 3. 41.2 years 4. 59.2(%) Females (remaining = males) 5. 6 weeks	DSM-IV Criteria	Sertraline: n=28	Duloxetine: n=26	Duloxetine initial therapy:20mg/day. Dose increments: 20mg/week. Mean Duloxetine dose: 55mg/day (range 20–60 mg/day Sertraline initial therapy:50 mg/day Dose increment: 50 mgweekly. The mean dosage of sertraline: 146 mg/day (range 50–200 mg/day)	None	HAM-D RS: Sertraline: 27.40 Duloxetine: 28.2	HAM-D RS: Sertraline: 17.43 Duloxetine: 19.32 ***p* = 0.463**	Sertraline group: Loss of appetite, gastric disturbance and sexual problems Duloxetine: Gastric disturbance, dizziness and decrease appetite
Friedli et al., 2017	RCT, Double blinded study	1. UK 2. 30 3. 59.06 years 4. 77(%) Males (remaining= females) 5.6 months	BDI-II	Sertraline: n=15	Placebo: n=15	Sertraline dose: 50mg MADRS was repeated at 2,4 and 6 months BDI-II: repeated at 6months	CKD patients on hemodialysis	BDI-II: Sertraline: 29.1±8.4 Placebo: 25.3	BDI-II Sertraline: 17.3± 12.4 Placebo: 10.2±5.8 ***p*=0.05**	Nausea, headaches, dizziness and insomnia

Author, Year	Study type	Study details	Diagnosis criteria of MDD	Pharmacological Intervention		Treatment regimen	Existing comorbid condition	Efficacy outcomes		Adverse events
		1.Origin of study, 2.Total subjects, 3.Mean age, 4.Sex 5.Length of study	*Clinical diagnosis of MDD*	*Treatment Group*	*Control group*	*Dosage and dose escalation details.*	*Presence of a chronic disorder along with MDD*	*At baseline*	*At the end of study* *p-value*	*Reported serious/mild adverse effects during trial*
Hantsoo et al., 2014	RCT, Double blinded study	1. USA 2. 38 3. 30.8±4.0 years 4. 100 (%) Females 5. 6 weeks	DSM-IV Criteria	Sertraline: n=17	Placebo: n=19	Sertraline: 50 mg or placebo daily to a max dose:200 mg/day.	None	HAM-D RS: Sertraline 21.9 Placebo 22.3	HAM-D RS Sertraline 8.8 Placebo 13.0 ***p*=0.03**	Sertraline group: nausea (n =3;17.6 %), headache (n =1; 5.8 %), and diarrhea Placebo: 1 subject frequent diarrhea
Greenberg et al., 2020	RCT, Double blinded study	1. USA 2. 222 3. 36.5 Years 4. 148 Females (remaining = males) 5. 8 weeks	QIDS-SR score ≥ 14	Sertraline: n=110	Placebo: n=112	N/A	None	HAM-D RS: Sertraline 18.75 Placebo: 18.9	HAM-D RS: Sertraline: 9.8 Placebo: 14.0 ***p=0.05***	N/A
O'Connor et al., 2010	RCT, Double blinded study	1.USA 2. 469 3. 62.9 years 4. 101 Females (remaining = males) 5.12 weeks	DSM-IV Criteria	Sertraline: n=234	Placebo: n=235	Sertraline 50 to 200 mg/day versus matching placebo for12 weeks	CHF	HAM-D RS: Sertraline: 18.3 Placebo: 18.4	HAM-D RS: Sertraline: 11.8 Placebo: 11.5 ***p*<.001**	N/A

Author, Year	**Study type**	**Study details**	**Diagnosis criteria of MDD**	**Pharmacological Intervention**		**Treatment regimen**	**Existing comorbid condition**	**Efficacy outcomes**		**Adverse events**
		1.Origin of study, 2.Total subjects, 3.Mean age, 4.Sex 5.Length of study	***Clinical diagnosis of MDD***	***Treatment Group***	***Control group***	***Dosage and dose escalation details.***	***Presence of a chronic disorder along with MDD***	***At baseline***	***At the end of study*** ***p-value***	***Reported serious/mild adverse effects during trial***
Valle-Cabrera et al., 2018	RCT, Double blinded study	1. Cuba 2. 77 3. 45.2 4. 71 (Females) (remaining = males) 5. 10 weeks	DSM-IV Criteria	Sertraline: n=39	Placebo: n=38	Sertraline fixed dose of 50mg, flexible dose upto 200 mg/d	None	HAM-D RS: Sertraline 22.9 Placebo 23.3	HAM-D RS: Sertraline 6.9 Placebo 13.3 ***p* < 0.0001**	Sertraline arm: headache, diarrheas, and weight loss.
Kamijima et al., 2006	RCT, Double blinded study	1. Japan 2. 235 3. 52 4.74(Females) (remaining = males) 5. 16 weeks	DSM-IV Criteria	Sertraline: n=117	Placebo: n=118	Sertraline 50–100mg/day	None	HAM-D RS: Sertraline and Placebo: 22.3	HAM-D RS: Sertraline: 6.3 Placebo: 9.2 ***p*=0.016**	Sertraline group: dizziness (2.6%), dry mouth (2.6%), diarrhea (2.6%) and upper abdominal pain (2.6%), somnolence(3.4%), headache(3.4%),

Author, Year	**Study type**	**Study details**	**Diagnosis criteria ofMDD**	**Pharmacological Intervention**		**Treatment regimen**	**Existing comorbid condition**	**Efficacy outcomes**		**Adverse events**
		1.Origin of study, 2.Total subjects, 3.Mean age, 4.Sex 5.Length of study	***Clinical diagnosis ofMDD***	***Treatment Group***	***Control group***	***Dosage and dose escalation details.***	***Presence ofa chronic disorder along with MDD***	***At baseline***	***At the end of study*** ***p-value***	***Reported serious/mild adverse effects during trial***
Hedayati et al., 2017	RCT, Double blinded study	1. USA 2. 201 3. 58.2 4. 27(%) Females (remaining = males) 5. 12 weeks	DSM-IV Criteria	Sertraline: n=102	Placebo: n=99	Sertraline initial dose of 50 mg/d (max dose: 200 mg/d based on tolerability& response	Non dialysis CKD	QIDS-C16: Sertraline: 14 Placebo: 14.2	QIDS-C16: Sertraline: 9.8 Placebo: 9.2 **p = 0.82**	Sertraline arm: headache, diarrheas, and weight loss.
Fann et al., 2017	RCT, Double blinded study	1. USA 2. 62 3. 58.2 4.14 Females (remaining = males) 5. 12 weeks	PHQ-9 and DSM-IV Criteria	Sertraline: n=31	Placebo: n=31	Sertraline initial dose of 25mg (max dose: 200 mg/d based on tolerability& response)	None but TBI present in patients	HAM-D RS: Sertraline: 23.1 Placebo: 22.7	HAM-D RS: Sertraline: 16.2 Placebo: 14.8 ***P*<.006**	Sertraline: Dry mouth, sweating, dizziness, headache, sedation, somnolence, diarrhea
He et al., 2016	RCT, Double blinded study	1. China 2. 120 3. 60.2 4. N/A 5. 6 weeks	DSM-IV Criteria	Sertraline: n=60	Placebo: n=60	Sertraline Hcl Tab:50mg/day for 6 weeks+ COPD treatment	COPD	HAM-D RS: Sertraline: 24.4 Placebo: 25.1	HAM-D RS: Sertraline: 2.0 ± 0.9ggb Placebo: 3.8 ± 1.2 ***p*< 0.05**	N/A

Author, Year	**Study type**	**Study details**	**Diagnosis criteria of MDD**	**Pharmacological Intervention**		**Treatment regimen**	**Existing comorbid condition**	**Efficacy outcomes**		**Adverse events/comments**
		1.Origin of study, 2.Total subjects, 3.Mean age, 4.Sex 5.Length of study	***Clinical diagnosis of MDD***	***Treatment Group***	***Control group***	***Dosage and dose escalation details.***	***Presence of a chronic disorder along with MDD***	***At baseline***	***At theend ofstudy*** ***p-value***	***Reported serious/mild adverse effects during trial***
Ch et al., 2022	RCT, Double blinded study	1. India 2. 81 3. 46.5 4.29 Females (remaining = males) 5. 4 weeks	DSM-V Criteria	Sertraline: n=42	Desvenl afaxine (Des): n= 39	Desvenlafaxine Group: Majority (77%) of them were taking a dosage of 100 mg. Sertraline group: Majority (74%) of them were taking a dosage of 50 mg.	None	HAM-D RS Sertraline: 17.6905 Des: 17.1282	HAM-D RS Sertraline 8.4048 Des: 9.5385 ***p*<0.00001**	Adverse events not monitored ***Comment:*** Sertraline showed a better clinical outcome when compared to desvenlafaxine
Lustman et al., 2006	RCT, Double blinded study	1. US 2. 152 3. 58.2 4. 91 Females (remaining = males) 5. 16 weeks	DSM-IV Criteria	Sertraline: n=79	Placebo: n=73	Mean dose of Sertraline given 117.9g/d	Type II Diabetes Mellitus	HAM-D RS Sertraline 15.7 ± 4.9 Placebo 15.9 ± 3.8	HAM-D RS Sertraline 3.3 ± 2.7 Placebo 4.0 ± 3.5 ***p* = 0.02**	Adverse events not reported ***Comments:*** Sertraline beneficial than placebo in preventing recurrence of depression in diabetic patient
Shelton et al., 2006	RCT, Double blinded study	1. USA 2. 160 3. 39.3 4. 85 Females (remaining = males) 5. 8 weeks	DSM-IV Criteria	Sertraline: n=82	Venlafaxine XR: n=78	Sertraline dose: 150 mg/day Venlafaxine dose: 225 mg/day	None	HAM-D RS Sertraline 22.1 Venlafaxine 22.4	HAM-D RS Sertraline 10.8 Venlafaxine 9.7 **No significant difference**	Headache, nausea, insomnia, genitourinary side effects, sexual side effects. ***Comments:*** both drugs equally effective

Chapter 4

Discussion

The systematic review addresses the efficacy of Sertraline for the treatment and management of MDD exclusively among adult population through endpoint assessment with the evaluation of statistical data, a prominent difference; both statistically significant and some statistically insignificant results were obtained. This shall allow the readers to identify the clinical effectiveness of Sertraline therapy in MDD. However, there are several studies conducted in this field such as the one conducted by Wagner et al. (2003) that evaluates the efficacy of sertraline among a different population group such as children and adolescents. Another aspect of difference that has been observed within the present study is the incorporation of studies that assess the efficacy of Sertraline combined with a different pharmacological intervention as shown in the studies by Cooper-Kazaz et al. (2007) and Moret (2005). Apart from this, there are numerous studies that also evaluates the efficacy of Sertraline comparing it with herbal treatments such as the one done by Ahmadpanah et al. (2019) which were not a part of the inclusion criteria of the present systematic review. However, the review has compiled RCTs conducted in the major continents such as in Asia, North America, South America, and Europe but one significant drawback of the review is the absence of RCTs assessing clinical effectiveness of Sertraline in African and Australian continent along with Antarctica as well. Another limitation of the study is the absence of careful evaluation of dropout rates of subjects in each study which were not detailed in most of the studies. Since a recent study has identified the widespread increase of MDD among different age groups of all sexes it has become essential to evaluate numerous more RCTs to generate stronger evidence supporting the effectiveness of Sertraline in the treatment and management of

MDD among different population groups as well as ethnicity along with impact of combination therapies on clinical effectiveness. (Goodwin et al., 2022)

Chapter 5

Conclusion

Though the clinical efficacy of Sertraline or any other antidepressants are evaluated using several rating scales, HAM-D rating scale, the most commonly used “gold-standard” scale is the basis of clinical efficacy evaluation of Sertraline and the comparator in all the 13 studies of the present review which allows the investigator to easily examine the efficacies of both groups. By assessing the scores at baseline and at the end of the study, outcomes of treatments were evaluated along with adverse events that were presented by the subjects. Furthermore, majority of the studies showed a statistically significant difference in their outcomes. Therefore, it can be safely concluded that the use of Sertraline among patients with MDD had shown to improve symptoms associated with depression. However, due to the complex and multifactorial etiology of MDD, there are prevalence of certain knowledge gaps which needs to be investigated by carrying out increasing number of studies in relevant field.

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