A Systematic Review on the Efficacy of Fluoxetine in the Management of Anxiety Disorders

By

Rabia Akter
19346008

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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.

Student's Full Name & Signature:

Rabia Akter
19346008

Approval

The thesis titled “A Systematic Review on the Efficacy of Fluoxetine in the Management and Treatment of Anxiety Disorders” submitted by Rabia Akter (19346008) of Summer, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on December 2023.

Supervised By:

Supervisor:

_____

Dr. Eva Rahman Kabir
Professor and Dean, School of Pharmacy
Brac University

_____

Syeda Maliha Ahmed
Lecturer, School of Pharmacy
Brac University

Approved By:

Assistant Dean & Program Coordinator:

_____

Dr. Hasina Yasmin
Professor, Assistant Dean and Program Director
School of Pharmacy
Brac University

Dean:

_____

Dr. Eva Rahman Kabir
Professor and Dean, School of Pharmacy
Brac University

Ethics Statement

The project does not use any animal models. So, no animals were involved or harmed. Additionally, there were no involvement of human participants as well and thus informed consent is not applicable.

Abstract

The quality of life and well-being around the world is hampered by a widely prevalent mental health disorder called anxiety. Anxiety disorder is a spectrum of various conditions including Generalized Anxiety Disorder (GAD), panic disorder, and agoraphobia. Selective serotonin reuptake inhibitors (SSRIs) have emerged as a prominent pharmacological intervention for managing anxiety and related depressive symptoms wherein Tricyclic Antidepressants (TCAs) and Benzodiazepines were primarily used. Effective options across the SSRI group of antidepressants have shown potential when given alone or with other therapies. The purpose of this study is to evaluate the effectiveness of Fluoxetine by evaluating journal articles with the help of established measurement scales. A wide number of Randomized Clinical Trials (RCTs) were identified among which nine studies were selected based on the predefined eligibility criteria. The quality of the studies taken was evaluated by assessing the risk of bias of each RCT incorporated in the systematic review. Comparisons were made between the treatment and comparator groups based on the result after intervention.

Keywords: SSRIs (Selective Serotonin Reuptake Inhibitors); Fluoxetine; RCT (Randomized Clinical Trail); Risk of Bias; Anxiety Disorder; Efficacy.

Acknowledgement

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Dedication

Dedicated to my respected faculty members, family and friends.

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List of Acronyms

GAD	Generalized Anxiety Disorder
FLX	Fluoxetine
PLA	Placebo
DB	Database
SSRI	Selective Serotonin Reuptake Inhibitor
HAM-A	The Hamilton Anxiety Rating Scale
HAM-D	The Hamilton Depression Rating Scale
BSPS	The Brief Social Phobia Scale
CGI-S	Clinical Global Impression – Severity
SCARED-P	Screen for Child Anxiety Related Emotion Disorder
PARS	Pediatric Anxiety Rating Scale
HADS	Hospital Anxiety and Depression Scale
SPAI	Social Phobia and Anxiety Inventory

Chapter 1

Introduction

Anxiety is a mental illness**,** a feeling of fear, dread, and uneasiness. If it is not occasional then it is considered a disorder and there are different types of it such as generalized anxiety disorder (GAD), panic disorder, social anxiety disorder, specific phobias (heights, flying), agoraphobia, separation anxiety, selective mutism, medication-induced anxiety disorder, etc. Common symptoms of an anxiety disorder include panic, fear, the feeling of danger, sleep disturbance, inability to concentrate, over-excitement, hyperventilation, dry mouth, fast heart rate, etc. According to a study on mental health in Australia, the prevalence of anxiety disorders based on the age group is 9% in males and 22% in females among the age range of 16-24 years (Slade et al., 2009). On the other hand, among the age range of 25-34 years, 12% of males and 21% of females suffer from anxiety, within the range of 35-44 years, 14% of male and 21% of female candidates face anxiety symptoms. In the age range of 45-54 years, 13% of males and 21% of females show signs related to anxiety disorder. In the age range of 55-64 years, 8% of the males and 13% of the females develope an anxiety disorder and finally the old adult group with age of 65+ years, 4% of males and 6% of female candidates suffer from anxiety and which indicates very less prevalence in the old adult group (Slade et al., 2009)**.** The result also indicates anxiety disorders are more common in female than that of male candidates.

1.1 Etiology & Pathophysiology of Anxiety

Although the precise cause is not known, it can occur due to genetic history, environmental stress, drug withdrawal, or misuse along with other medical conditions. Children's anxiety may be a common occurrence. Seven to nine months of age is when stranger anxiety first appears (Amray et al., 2019). It is considered that the central nervous system's ability to modulate behaviour is impaired when anxiety and associated illnesses arise. Increased sympathetic

arousal of various intensities leads to the physical and emotional symptoms of this dysregulation (Kaplan and Sadock, 1995).

Numerous neurotransmitter systems have been suggested to have a part in one or more of the related modulatory processes. The serotonergic and noradrenergic neurotransmitter systems are mostly taken into account. Increasing evidence supports the role of aberrant serotoninergic and noradrenergic neurotransmission in somatic symptoms. The physiological alteration underlying the diminished serotonin (5-HT) and norepinephrine (NE) signalling may contribute to impaired signal transduction, reduced 5-HT, or NE release from terminals of presynaptic neurons, and result in alterations in function and/or number of receptors and changes in intracellular signal processing (Amray et al., 2019; Nemeroff, 2000). Other pathways and neuronal circuits in other parts of the brain govern and are regulated by these systems, leading to dysregulation of physiological arousal and the emotional experience of this arousal (Nemeroff, 2000). Many consider that its development is caused by low serotonin system activity and high noradrenergic system activity. Therefore, the first-line treatment for it is a combination of selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) (Amray et al., 2019). Because many illnesses on the anxiety spectrum respond well to benzodiazepine therapy, disruption of the gamma-aminobutyric acid (GABA) pathway has also been suggested (Nutt, 2001). The function of corticosteroid regulation and its connection to anxiety and terror symptoms have drawn some attention. Corticosteroids may alter the activity of certain neural circuits, which may impact not just behaviour under stress but also how the brain processes cues that cause anxiety (Korte, 2001). The neurotransmitter cholecystokinin has long been thought to play a role in controlling emotional states (Korte, 2001). Moreover, some of the common environmental factors such as exposure to stressful situations, the occurrence of panic attacks most often as well as reaction to traumatic events, and social isolation develop anxiety in an individual. Besides, according

to most researchers explained that anxiety might occur due to genetic predispositions. Although it is not claimed that genetic predisposition has the inevitability of causing anxiety symptoms in generations, 30% of the risk is attributed to genetic factors; several genes have shown involvement in increasing the risk for anxiety disorders, for instance, SLC6A4, 5-HTTLPR, FKBP5 and GABARA (Korte, 2001).

1.2 Prevalence of Anxiety Disorder

Anxiety disorders are extensive throughout the world. According to a systematic review on the approximation of anxiety disorder in the global burden of disease was conducted on 204 countries and regions from 1990 to 2019 which gave result about the outbreak, prevalence and disability-adjusted life years (DALYs) among the different countries. Around the world, 45.82 million [95% uncertainty interval (UI): 37.14, 55.62] incident cases of anxiety disorders, or 301.39 million (95% UI: 252.63, 356.00) predominant cases and 28.68 million (95% UI: 19.86 (39.32) DALYs were analyzed in 2019 (Yang et al., 2021). The latest absolute number of anxiety disorders increased by 50% from 1990, despite the fact that the overall age-standardized burden rate of anxiety disorders remained stable for the previous three decades. Both the age-standardized burden rate and the changing trend of anxiety disorders by gender, country, and age varied greatly, according to the findings. In 2019, 7.07% of the worldwide DALYs because of nervousness issues were owing to bullying victimization, fundamentally among the age group of 5-39 years, and the extent expanded in practically all countries and regions compared with 1990 (Yang et al., 2021).

1.3 Mechanism of Action of Fluoxetine

Selective Serotonin Reuptake Inhibitors (SSRIs) are the first choice of drug in treating anxiety disorders and related depressive disorders. Fluoxetine is one of most significant SSRIs class. It is sold under the brand name “Prozac” worldwide. It was discovered by Eli Lilly and Company

in 1972 and used medically in 1986. Fluoxetine got FDA approval in December 1987 and available in the market from January 1988. It gives pharmacological action by inhibiting serotonin reuptake into presynaptic serotonin neurons by stopping the reuptake transporter protein situated in the presynaptic terminal as shown in figure 1. As a result, serotonin concentration increases in synapses which stimulate more receptors and hence mood is enhanced. Fluoxetine may also influence the action at 5HT2A and 5HT2C receptors (GPCRs) to regulate the effect of compounds influencing anxiety, depression, schizophrenia, hallucinations and some other types of mood-related disorders (Sohel et al., 2022).

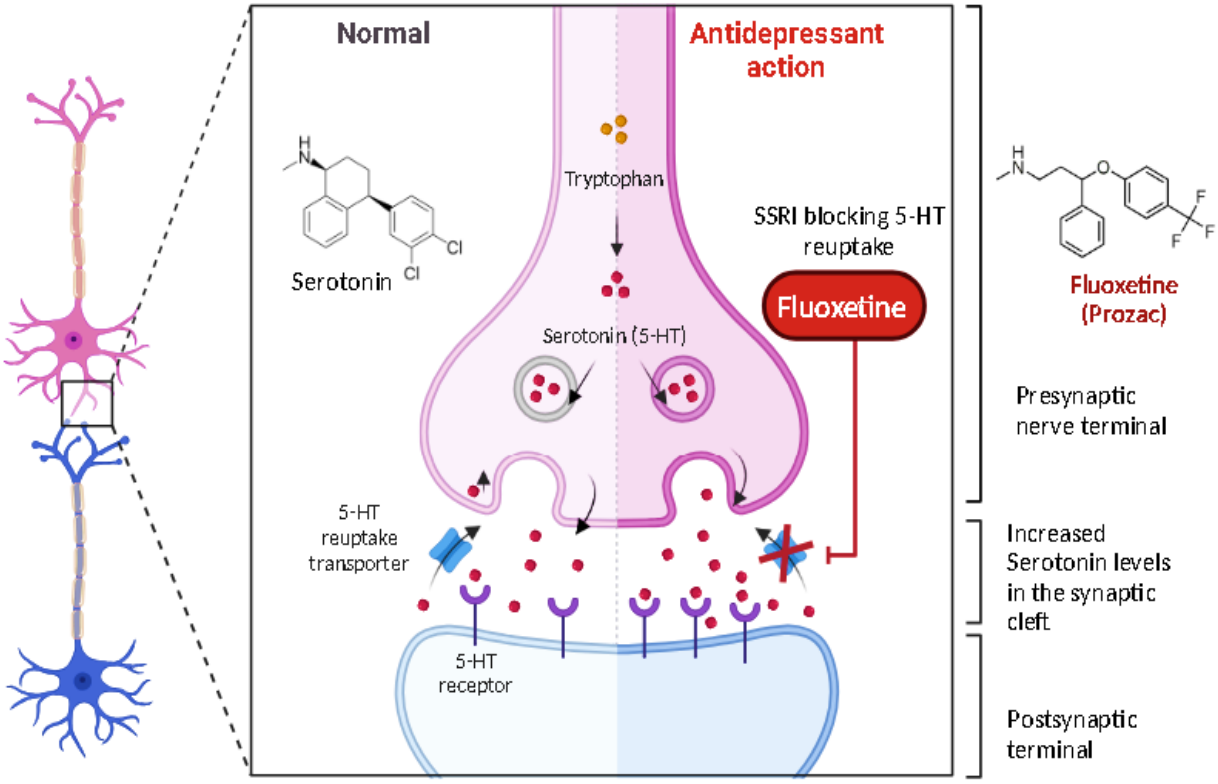

Figure 1: Mechanism of Action of Fluoxetine (Figure generated by Biorender)

Chapter 2

Methods and Materials

2.1 Search Strategies

PubMed database was used for collecting journal articles that presented Real World Data (RWD) related to the efficacy of Fluoxetine in the treatment and management of anxiety among participants administered with Fluoxetine. A search string was generated using some major keywords like “Anxiety”, “GAD (generalized anxiety disorder)”, “Panic Disorder”, “Efficacy”, “Fluoxetine”, “Prozac” etc as shown in table 1. The Boolean logic “and” and “or” were used to combine the keywords and make the search more appropriate. Efficacy of the drug is determined in case of anxiety along with some comorbid situation as well. Filters were also applied to generate a more specific search result taking into consideration the inclusion and exclusion criteria as well.

Table 1: List of Search Keywords

Number	Search Term
1	Fluoxetine
2	Prozac
3	Efficacy
4	Anxiety
5	Anxiety disorders
6	Generalized Anxiety Disorder
7	Phobia
8	RCT
9	Blind
10	Double blind
11	Children
12	Adults
13	Treatment

The search string used was, (“Fluoxetine” [MeSH Terms] OR “Fluoxetine” [All Fields] OR “Prozac” [All Fields]) AND (“Anxiety Disorder” [MeSH Terms] OR (“Anxiety” [All Feilds]

AND “Disorder” [All Fields]) OR “Generalized Anxiety Disorder” [All Fields] OR “GAD” [All Fields]) AND (“Efficacy” [All Fields] OR “Effectiveness’ [All Fields]). Some other filters were also applied:

- Text availability: Full texts
- Type of articles: RCTs and clinical trials
- Time frame: 1995-2023
- Species: Human

2.2 Criteria for Selection of Articles

Some inclusion and exclusion criteria were followed to extract the journal articles that include the efficacy of Fluoxetine, comparison of Fluoxetine with other medications, outcome/result based on the efficacy, for instance, HAM-A, CGI-S, HAM-D, SCARED, PARS etc. The inclusion and exclusion criteria are shown in table 2. The flow of identification of articles via database is shown using a PRISMA flow diagram in figure 2. Only the Randomized Clinical Trials (RCTs) were included to observe the efficacy of Fluoxetine for anxiety or GAD. Unqualified studies for example nonclinical trials, reviews, uncontrolled trials, case control studies, quasi-RCTs are eliminated. The efficiency of Fluoxetine was observed on diagnosed patients irrespective of race and gender. Patient were either treated with Fluoxetine as monotherapy or combination therapy. The selected studies had control groups who were either under placebo treatment or behavioural therapies (BMT, QoL). Studies that state the efficacy of the drug either for anxiety disorders or along with a comorbid disease like selective mutism, VVS, cancer were also included. Even though majority of the studies did not identify the presence or absence of any existing comorbidity among the patients.

Table 2: Inclusion and Exclusion Criteria

Parameters	Inclusion Criteria	Exclusion Criteria
Patient	Patients diagnosed with anxiety disorders with or without comorbid situations.	Unconscious patients and treatment resistant patients Patient without any symptoms of the anxiety disorders.
Intervention	Fluoxetine as monotherapy or combination therapy (with placebo, different kinds of behavioural therapy).	Trials showing results for other kinds of SSRIs (for example, citalopram, sertraline etc), Homeopathy treatments.
Comparator	Placebo effects or effects of behavioural therapies (BMT, QoL).	Intervention like physiotherapy, exercise, surgical interventions, etc in the control group were not included.
Studies	Trial type: Randomized Clinical trial Time frame: 1995-2023 Language: English Website: PubMed	Animal studies/trials, Clinical trials, Literature reviews, Studies that are not published in English language Studies not presenting any kind of anxiety disorders.

2.3 Outcome Measurement

For assessing the outcome at the baseline (primary) and at the end of the study (secondary), some scoring systems or scales are used such as HAM-A, CGI-S, SCARED-P, HADS to diagnose the disease. A 50% or higher reduction in the scores after being administered with an antidepressant is usually on indicator of clinical efficacy whereby suggesting a positive response to the treatment assigned.

2.4 Quality Assessment

The Cochrane Risk of Bias 2.0 (RoB 2) tool was utilized to determine the risk of bias of all the selected nine articles included for the systematic review. The tool assessed the articles based on five domains that includes randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. All the five domains of the tool were assessed separately for each study in order to generate an overall bias, hence assessing the quality of the studies. Randomization of selected studies was done and risk of bias was assessed by the risk of bias graph and the overall risk of bias of individual studied using traffic light plot given by the RoB 2 tool.

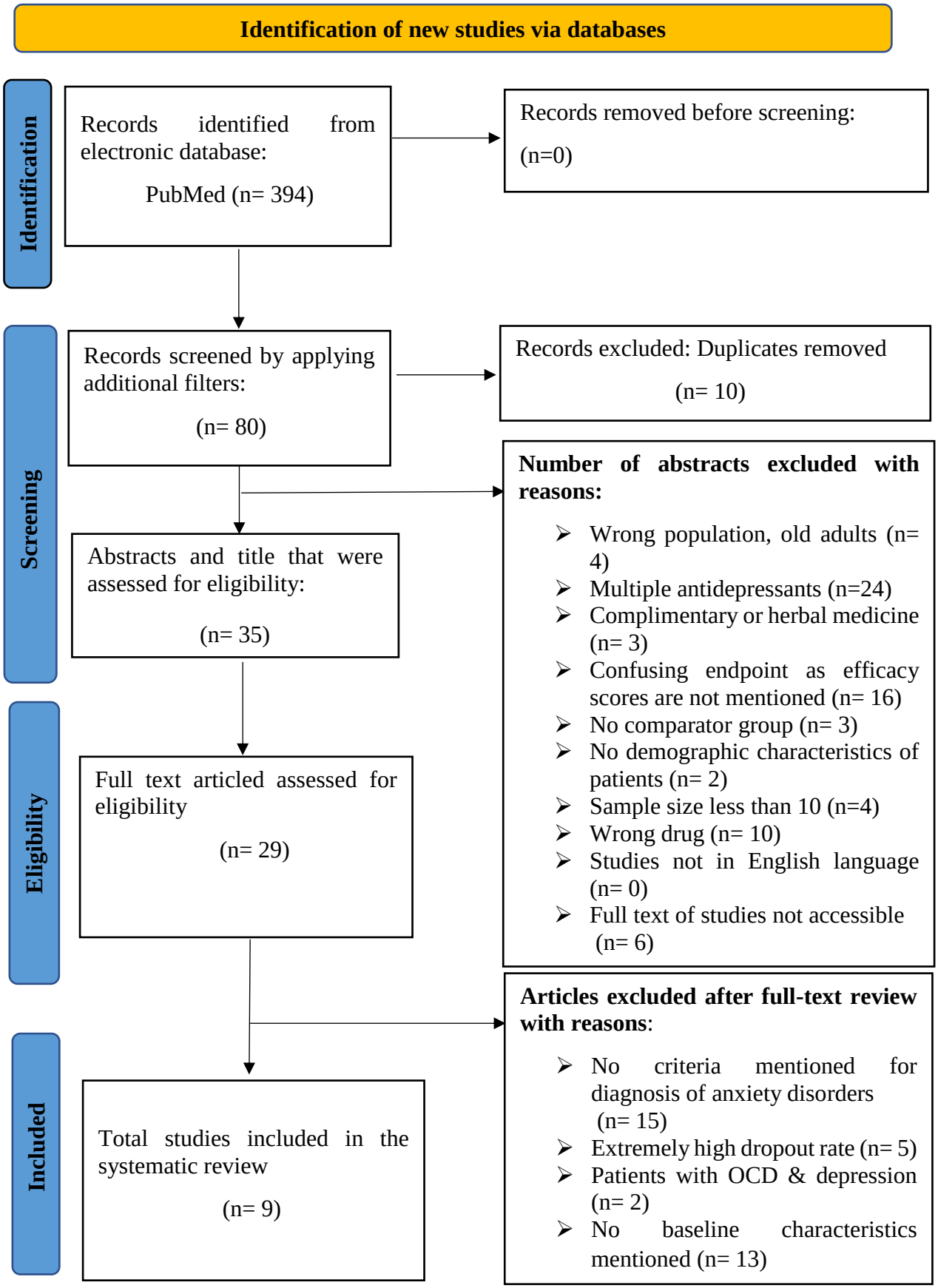

Figure 2: Preferred Reporting Items for Systematic Review and d Meta-Analysis (PRISMA) Flow Diagram

Chapter 3

Results

For the systematic review, PubMed was searched for journal articles on the effectiveness of Fluoxetine. According to the exclusion and inclusion criteria, studies were included by screening the title, abstract and full text. The selected language was English and reviewed journals were prioritized. Data table that summarised the most important details of each article was created by highlighting the most significant details such as the first author, study details that included origin of trial and patient characteristics, treatment regimen, diagnostic criteria, pharmacological intervention and last but not the least efficacy outcome (table 3). The outcome of the intervention was measured by using some established scoring systems that include HAM-A, GAD-7, CGI-S, PARS, PSWQ, SCL-90-R. Patient conditions were evaluated by evaluating the difference in the scores before the intervention and after the intervention. Only patients diagnosed with anxiety according to some published scoring systems were selected including patients with comorbid conditions. The nine studies were incorporated that matched with the requirements of the inclusion and exclusion criteria where all of them either single or double blinded RCTs, majority of them being double blinded. The method of eligibility as well as the step-by-step screening process that led to the careful selection of the nine DB journal articles is represented with the help of a PRISMA flowchart. It schematically represents the number of texts included, number of duplicate texts removed using Rayyans (10 duplicates were found) and number of texts that were excluded with reasons for each respectively.

Table 3: Characteristics of Studies and Participants

Article No.	Citation	Study Type	Study Details	Diagnostic Criteria	Treatment Option & Pharmacological Intervention	Efficacy Outcome
1	(Costa et al., 2021)	Three-Arm RCT; Single blind	Total subject= 249(223 were analyzed), Age(mean)= 35.28 (±12.47), Length of study= 8 weeks, Origin of study= Brazil	GAD-7[1] Scale, HAM-A, PSWQ, QoL, WHOQoL-BREF	FLX 20–60 mg/day (Initial dose 20 mg); **Treatment group-** FLX: n=81**Control group/Comparator-** BMT: n=84, QoL: n=84	**At baseline [mean (SE)]-** HAM-A: 30.70 (0.7) (FLX), 29.69 (0.8) (QoL), 29.91 (0.8) (BMT)[1] **At the end of study [mean (SE)]-** HAM-A[1]: 17.60 (1.4) (FLX) FLX>QoL p = 0.007, 22.46 (1.5) (QoL),21.10 (1.4) (BMT). P= 0.054
2	(Flevari et al., 2017)	RCT Double Blind	Total subject= 60, Age (mean)=392±.4 (FLX) 41±2.5 (Pla), Length of the study= 12 months, Origin of study= Greece. **Existing comorbid situation= vasovagal syncope (VVS)**	ASI-Questionnaire, HUT	FLX 10-40 mg/day (Initial dose 10 mg); **Treatment group-** FLX: n= 40 **Control group/Comparator-** Placebo: n= 20	**At baseline[mean]-**History of syncope spells (n)= 6±0.9 (FLX), 5±1.0 (Pla); History of presyncope spells (n)= 8±2.3(FLX), 9±2.1 (Pla) **At the end of study[mean]-**History of syncope spells (n)=2±0.2 (FLX), 2±0.3 (Pla); History of presyncope spells (n)=4±0.2(FLX), 5±0.7(Pla)P < 0.05
3	(Barteria n et al., 2018)	RCT Double Blind	Total subject= 15, Age= 5-14 years, Length of study= 12 weeks, **Existing comorbid situation= selective mutism with social anxiety**	CGI-S[1], MASC-2: SAS, SMO	FLX 10-20 mg/d (initial dose 10 mg/d); **Treatment group-** FLX: n= 6 **Control group/Comparator-** Placebo: n= 9	**At baseline [mean (SD, Range)]-** **DBR:** Social engagement 0.82 (1.84, 0-10), Responsive speech 0.42 (1.72, 0-10), Spontaneous speech 0.11 (0.66, 0-5) **SMQ:** 11.09 (2.56, 5-14); **CGI-anxiety severity:**4.13 (0.80, 3-5) (mother),4.07 (0.33, 4-5) (psychiatrist) **At the end of study [mean (SD, Range)]- DBR:** Social engagement: 2.27 (2.80, 0-9) Responsive speech: 1.97 (2.75, 0-10) Spontaneous speech: 0.75 (1.59, 0-8) **SMQ:** 18.2 (4.59, 10 24); **CGI-anxiety severity:**4.07 (0.33, 4-5) (mother), 3.80 (0.42, 3-4) (psychiatrist), P < 0.05

[1] Body in Mind Training (BMT), Generalized Anxiety Disorder-7 (GAD-7) Scale, The Hamilton Anxiety Rating Scale HAM-A, The Penn State Worry Questionnaire (PSWQ), QoL, WHO Quality of Life (WHOQoL-BREF) instrument, Clinical Global Impression (CGI)

Article No	Citation	Study Type	Study Details	Diagnostic Criteria	Treatment Option & Pharmacological Intervention	Efficacy Outcome
4	(Clark et al., 2005)	RCT Double Blind	Total subject= 74, Age(mean)= 11.8 ± 2.8 years, Length of study= 1 year	SCARED-P, SCARED-C, PARS-P, PARS-C	FLX 10-20 mg/d (initial dose 10mg/d), Placebo; **Treatment group-** fluoxetine (n = 37) **Control group/Comparator-** placebo (n = 37)	**At baseline [mean (SD, Range)]- SCARED-P:** 21.3 ± 13.3, **SCARED-C:** 13.9 ± 13.6, **PARS-P:**13.4 ± 7.8, **PARS-C:** 8.4 ± 6.6 **At the end of study [mean (SD, Range)]- SCARED-P:** 13.7 ± 12.0, **SCARED-C:** 10.5 ± 13.8, **PARS-P:** 8.6 ± 6.8, **PARS-C:**5.6 ± 5.2. P < 0.05
5	(Razavi et al., 1996)	RCT Double Blind	Total subject= 115 (69 continued the study), Length of study= 5 weeks, **Existing comorbid situation=** Cancer	HADS, SCL 90-R total score	FLX 20 mg/d, Placebo; **Treatment group-** fluoxetine (n = 30) **Control group/Comparator-** placebo (n = 39)	**At baseline [mean (SD, Range)]- HADS[2] total score:** 23.5 (15.5) (PBO), 22.7 (6.0) (FLX); **SCL 90-R total score**: 1.1 (0.5) (PBO), 1.1 (0.5) (FLX) **At the end of study [mean (SD, Range)]- HADS total score**: 17.5 (7.4) (PBO), 15.0 (6.1) (FLX), **SCL 90-R total score**: 0.7 (0.5) (PBO), 0.6 (0.4) (FLX) P= 0.02
6	(Davidson et al., 2004)	RCT Double Blind	Total subject= 295, Age=37.1 years (mean), Length of study= 14 weeks, Origin of Study= Durham, NC.	Cognitive behavioural therapy weekly for 14 sessions; CGI-S, BSPS, SPAI[2]	FLX and Placebo 10 mg/d-60 mg/d (initial dose 10mg/d); **Treatment group-** FLX (n= 57), CCBT (n= 60), CCBT/FLU (n= 59), CCBT/PBO (n= 59) **Controlled group-** PBO (n= 60)	**At baseline [mean (SE)]- CGI-S[2] Score:** 4.4 (0.1) (FLX), 4.5 (0.1) (CCBT), 4.4 (0.1) (CCBT/FLX), 4.4 (0.1) (CCBT/PBO), 4.3 (0.1) (PBO) **SPAI Score:** 97.5 (24.8) (FLX), 106.1 (21.3) (CCBT), 109.9 (23.8) (CCBT/FLX), 111.3 (21.0) (CCBT/PBO), 112.0 (21.0) (PBO). **At the end of study [mean (SE)]- CGI-S Score:**2.7 (1.2) (FLX), 2.9 (1.2) (CCBT), 2.7 (1.2) CCBT/FLX), 2.8 (1.2) (CCBT/PBO), 3.3 (1.3) (PBO). **SPAI Score:** 69.3 (37.2) (FLX), 77.1 (28.7) (CCBT), 76.1 (31.5) (CCBT/FLX), 75.4 (32.0) (CCBT/PBO), 94.8 (28.0) (PBO). P = 0.03

[2]Hospital Anxiety and Depression Scale (HADS), Clinical Global Impression – Severity (CGI-S), Social Phobia and Anxiety Inventory (SPAI)

Article No	Citation	Study Type	Study Details	Diagnostic Criteria	Treatment Option & Pharmacological Intervention	Efficacy Outcome
7	(Michelson et al., 1999)	RCT Double Blind	Total subject= 80, Age (mean s.d.) = 38.7(9.5) (FLX), 36.4 (11.1) (PBO), Length of study= 24 weeks, Origin of Study= IN, USA.	HAM-A[3], HAM-D, SCL-90-R[3]	FLX 10 and 20 mg/d; **Treatment group-** FLX (n= 38) **Control group/Comparator-** placebo (n = 50)	**At baseline [mean (s.d.)]- HAM-A Score:** 7.3 (4.2) (FLX), 8.4 (5.8) (PBO) **SCL-90-R:** 36.2 (34.5) (FLX), 47.0 (37.5) (PBO) **At the end of study [mean (s d.)]- HAM-A Score:**0.25 (5.14) (FLX), 3.28 (7.l2) (PBO) **SCL-90-R:** 0.42 (29.36) (FLX), 16.66 (37.43) (PBO) P= 0.012
8	(Michelson et al., 1998)	RCT Double Blind	Total subject= 243, Age (mean s.d.) =37.1 years, Length of study= 24 weeks, Origin of Study= IN, USA	HAM-A, HAM-D[4], CGI-S	FLX 10 and 20 mg/d; **Treatment group-** 10mg FLX (n= 84), 20mg FLX (n= 81) **Control group/Comparator-** placebo (n = 78)	**At baseline [mean (s.d.)]- HAM-A Score:** 17.4(8.0) (PBO), 18.1(7.0) (10mg FLX), 19.0(6.7) (20mg FLX). **At the end of study [mean (s.d.)]- HAM-A Score**: –5.3(7.8) (PBO), –7.3(7.6) (10mg FLX), –8.6(8.0) (20mg FLX)
9	(Birmaher et al., 2003)	RCT	Total subject= 74, Age (mean)= 11.8 ± 2.8 years, Length of study= 12 weeks, Origin of Study= Pennsylvania, US	PARS[4], CGAS, SCARED-P[4]	FLX 10mg -20mg (initial dose was 10mg); **Treatment group-** FLX (n= 37) **Control group/Comparator-** placebo (n = 37)	**At baseline [mean (SD, Range)]- PARS (5 items):** 15.6 ± 3.5(FLX), 14.9 ± 3.5(PBO); **SCARED-P total score:** 37.5 ± 11.9(FLX), 35.2 ± 12.0(PBO) **At the end of study [mean (SD, Range)]- PARS (5 items):** 7.1 ± 5.9(FLX), 9.3 ± 4.8(PBO); **SCARED-P total score:** 16.3 ± 12.7(FLX), 22.0 ± 12.3(PBO); P=0.004

[3] HAM-A: The Hamilton Anxiety Rating Scale, SCL-90-R: Symptom Checklist-90-Revised
[4] SCARED-P: Screen for Child Anxiety Related Emotion Disorder, PARS: Pediatric Anxiety Rating Scale, HAM-D: The Hamilton Depression Rating Scale

In the first article (Table 3), total subject of the study was 249 (223 were analyzed; adults), length of study was 8 weeks. Fluoxetine intervention is compared with patients that were treated with Body in Mind Training (BMT) program. The outcome was assessed by Generalized Anxiety Disorder-7 (GAD-7) Scale, The Hamilton Anxiety Rating Scale HAM-A, The Penn State Worry Questionnaire (PSWQ), QoL, WHO Quality of Life (WHOQoL-BREF) instrument. At the end of the trial, Fluoxetine was found to be superior to QoL which is statistically significant as p value is less than 0.05 here. At the same time, it was shown that BMT is both tolerable and effective as Fluoxetine **(P= 0.054**) (Costa et al., 2021).

In the second article (Table 3), the total subject of the study was 60, the length of the study was 12 months and there was an existing comorbid situation as well, called vasovagal syncope (VVS). Evaluation was made based on Addiction Severity Index (ASI)-Questionnaire and Head Up Tilt (HUT) testing. In respect of the arrangement of syncope free time during the study Fluoxetine gave more rate of recovery ($P < 0.05$; So, the result is statistically significant). Fluoxetine is superior to placebo against syncope in these patients (Flevari et al., 2017).

In the matter of record number 3 (Table 3), the total subject of the study was 15, length of study was 12 weeks and there was an existing comorbid situation called selective mutism with social anxiety. Efficacy of the intervention was evaluated in accordance with The Clinical Global Impression – Severity (CGI-S) scale, Direct Behavior Rating (DBR), Multidimensional Anxiety Scale for Children Second Edition™ (MASC-2): SAS, SMO. Fluoxetine was considered as highly acceptable medication and this result is statistically significant **($P < 0.05$).** However only two of the allocated children face minimal adverse effect (behavioral disinhibition) (Barterian et al., 2018).

Regarding article number 4 (Table 3), total subject of the study was 74, length of study was 1 year. The outcome is measured by The Hamilton Anxiety Rating Scale (HAM-A), The

Hamilton Depression Rating Scale (HAM-D) and Symptom Checklist-90-Revised (SCL-90-R) instrument. At the end of trial, treatment group has shown significant improvement with Fluoxetine intervention (**P < 0.05**; the result is statistically significant) (Clark et al., 2005).

In article number 5 (Table 5), total subject of the study was 115 (69 continued the study), length of study was 5 week and cancer existed as comorbid situation. Hospital Anxiety and Depression Scale (HADS), SCL 90-R total score was used to evaluate efficacy outcome. Fluoxetine was considered as more efficient in progressing global psychological adjustment. P value was 0.02 that means result is statistically significant (Razavi et al., 1996).

According to article number 6 (Table 3), total subject of the study was 295, length of study was 14 weeks. Cognitive behavioral therapy (CCBT) weekly for 14 sessions; CGI-S, The Brief Social Phobia Scale (BSPS), Social Phobia and Anxiety Inventory (SPAI). All of the applied interventions (FLU, CCBT) were superior to placebo and the result is significant (**P= 0.03)** (Davidson et al., 2004).

In accordance with record number 7 (Table), total subject of the study was 80, length of study was 24 weeks. Efficacy outcome was measured using HAM-A, HAM-D, SCL-90-R. Overall relapse rate was low. **P= 0.012** for SCL-90-R, hence the result is significant (Michelson et al., 1999).

In article number 8 (Table 3), total subject of the study was 243, length of study was 24 weeks. Efficacy was evaluated by using HAM-A, HAM-D, CGI-S. Increase in the symptoms of panic attack in case of 20mg Fluoxetine intervention was significant (**P= 0.04)** and patients treated with 10mg of Fluoxetine had more of the recovery rate (Michelson et al., 1998).

Finally, in article number 9 (Table 3), total subject of the study was 74, length of study was 12 weeks. PARS, CGAS, SCARED was used for efficacy outcome detection purpose. **P=0.004;**

Fluoxetine was effective in showing reduction in symptoms relating to anxiety disorders than that of the placebo group and the result is significant (Birmaher et al., 2003).

3.1 Risk of Bias Assessment

By the help of Cochrane Risk of Bias tool, ROB 2.0, risk of bias of all the included DB studies is measured wherein five domains were critically assessed that addressed a series of questions to evaluate bias. Each of the five domains were carefully analyzed that led to the generation of final judgments within the algorithm which labelled each of the nine DB studies as “low risk”, “high risk” and studies with “some concerns” respectively in figure 3 (Risk of Bias graph) and figure 4 (Overall Risk of Bias of Individual Studies Using "Traffic Light Plot”).

Risk of Bias Assessments:

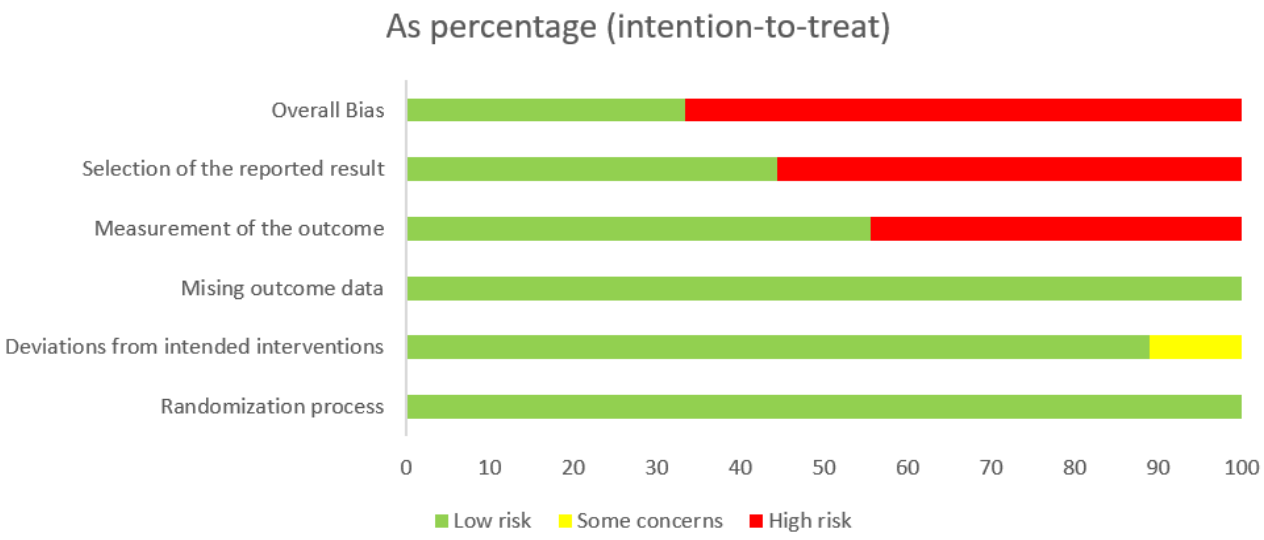

Figure 3: Risk of Bias

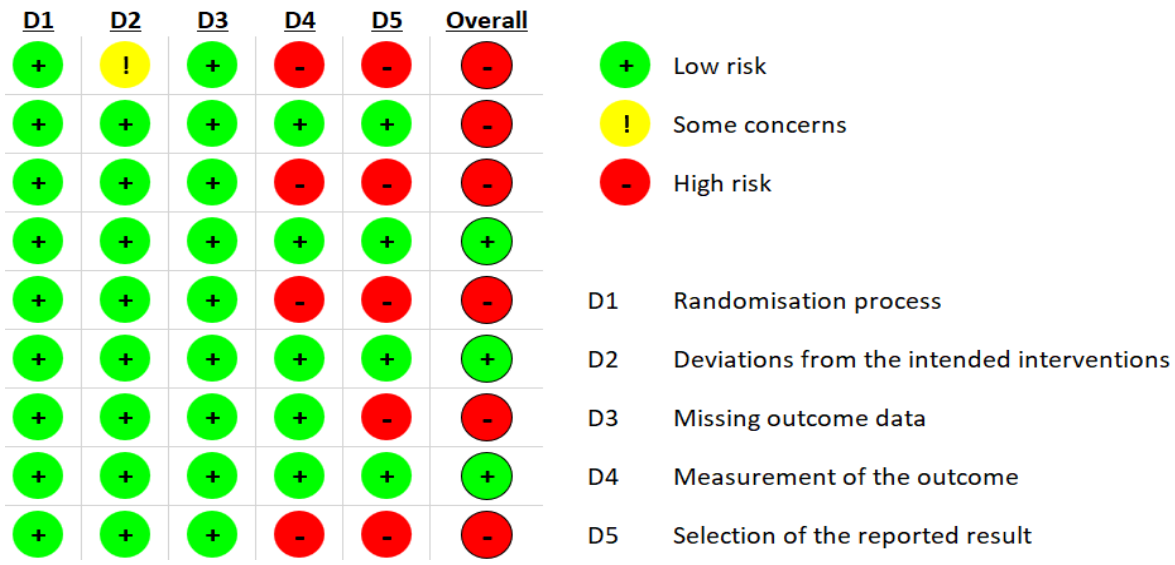

Figure 4: Overall Risk of Bias of Individual Studies Using "Traffic Light Plot"

Chapter 4

Discussion

In case of efficacy outcome of the first article, Fluoxetine and Body in Mind Training (BMT) program were regarded to be more efficient than that of the Quality of Life (QoL) program (Costa et al., 2021). The data from the second journal article (Flevari et al., 2017) and the third one (Barterian et al., 2018) revealed that Fluoxetine was found to be an acceptable medication although there were minimal chances of adverse events observed among very few candidates. Fluoxetine was more effective than that of the placebo-controlled outcomes and the results was statistically significant in both the study number 4 (Clark et al., 2005) and 5 (Razavi et al., 1996). Regarding the outcomes of study number 6, both fluoxetine and CCBT was effective in managing anxiety related behaviors (Davidson et al., 2004). The seventh and eighth journal articles revealed data wherein the investigators measured the effectiveness of Fluoxetine with placebo being used as the control in both. The outcomes favored Fluoxetine to be more reliable than that of placebo intervention (Michelson et al., 1999). Decrease in panic attack as indicated in the eighth journal article and its recurrence in subjects administered either fluoxetine or placebo were not that much related to overall clinical improvement (Michelson et al., 1998). But it was effective for the reduction of phobic avoidance, anxiety, depressive symptoms, and functional impairment. The final study of the systematic review, the ninth study also suggested that Fluoxetine can be considered as the first choice of drug in treating anxiety disorders and depression related syndromes (Birmaher et al., 2003). When it comes to management of mental disorders, there have been evidences which showcased that combination therapies such as incorporating IPT-interpersonal psychotherapy with Fluoxetine intervention may exert better outcome than that of single Fluoxetine administration which was highlighted in the study by Bozzatello & Bellino in the management of borderline personality disorder (BPD) (Bozzatello

& Bellino., 2016). A synergistic effect could be exerted by the Fluoxetine-Clonazepam co-therapy which has the potential to exhibit greater effectiveness than that of the monotherapy with Fluoxetine (Papakostas et al., 2010). Although the fact that synergistic effects could be observed with multiple pharmacological interventions or administering a pharmacologically active compound and therapies simultaneously, it was further explored in a clinical examination that addition of Fluoxetine with psychosocial treatment (dialectal behavior therapy) would not be able to exhibit a greater effect in case of borderline personality disorder (Simpson et al., 2004). In terms of side effect and tolerance profile, Fluoxetine is more tolerated and less frequent undesired adverse effects were observed by Fluoxetine in comparison with amitriptyline (Versiani et al., 1999). Another study showed that weight gain appeared as the more frequent adverse effect through mirtazapine consumption in comparison with Fluoxetine (Ribeiro et al., 2001). Another study unveiled that clomipramine can also be used instead of Fluoxetine as they have identical efficacy outcomes (Costa et al., 2013). When it comes to the management of depression along with anxious conditions, it was discussed that there were no greater differences in the pharmacological action among Fluoxetine, Sertraline and Paroxetine (Fava et al., 2000). There are some limitations regarding this systematic review including only RCTs were selected and the results were extracted from the selected studies and it was not about observing patients in person as we have to rely on the results from the studies provided by PubMed database. Taking into consideration that the aim of the systematic review was to address the specific research question regarding drug effectiveness of the selected drug but other concerns may also arise about the drug such as safety and quality journal articles as well as the concerns regarding biasness about the outcome also randomization might be incomplete in some cases (Jameson et al, 1991). Some advantages include, solve disputation among conflicting opinions and furnish well-grounded basis in making decisions.

Chapter 5

Conclusion

Among the selected nine studies, most of them indicated that Fluoxetine has shown significantly more efficient outcome by improving the overall patient condition suffering from anxiety related disorders and many other depressive symptoms. Several approved scales were used for the closest correct estimation of the efficacy outcome and based on the baseline scores as well as endpoint scores, inferiority of the interventions was assessed carefully. Beside this, side effects as well as adverse effects were also monitored during the trial period and this drug has shown least or no evidence of the unwanted effects.

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