Degree project

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Social Anxiety Disorder: SSRI vs. Placebo

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Abstract

Social anxiety disorder (SAD) is characterized by fear and avoidance of social interactions and situations in which an individual is being the focus of attention. This current thesis aims to examine the efficacy of pharmacological treatment, particularly selective serotonin reuptake inhibitors (SSRIs) in individuals with a generalized social anxiety disorder (gSAD) in comparison with placebo (no active medication). In this systematic review, Scopus and Web of Science were searched for relevant research regarding the efficacy of the SSRI medication (paroxetine, sertraline, fluvoxamine and escitalopram) in comparison with placebo. Sixteen articles were included in this analysis. Results demonstrated that SSRI medication has greater efficacy in comparison with placebo both in short- and long-term time, prevent relapse in the long-term treatment of SAD and had a beneficial effect on different areas of individuals life's such as work, performance, romantic relationships etc.

Keywords: SSRI, placebo, social anxiety disorder, generalized SAD, efficacy

Social Anxiety Disorder: SSRI vs. Placebo

Most people experience anxiety at some time in their lives but when anxiety becomes more than a temporary condition, it may develop into a disorder (Craske & Stein, 2016). Craske and Stein (2016) have identified several types of disorders: separation anxiety disorder, particular phobias, selective mutism, social anxiety disorder, panic disorder, agoraphobia, and generalized anxiety disorder; these common, debilitating conditions typically start in childhood, puberty or early adulthood. Social anxiety disorder (SAD) is characterized by fear and avoidance of social interactions and situations in which an individual is being the focus of attention. That avoidance can lead to marked distress and impairment in daily functioning (Stein & Stein, 2008). Fear of negative judgment from others, as well as physical symptoms such as blushing, fear of vomiting, are all listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as characterized symptoms of SAD (Craske & Stein, 2016). Socially anxious individuals (refers to individuals diagnosed with a social anxiety disorder) in clinical settings can be divided into two subtypes: with specific or generalized social anxiety disorder (Craske & Stein, 2016). My focus concerns individuals with generalized SAD (gSAD) who fear and avoid a wide range of social circumstances; in contrast, individuals with specific SAD avoid specific situations such as speaking in public (Craske & Stein, 2016).

One of the earliest developmental markers of social anxiety is behavioural inhibition (BI), a temperamental characteristic that refers to a child's responses when faced with new circumstances or unknown people (Craske & Stein, 2016). SAD, which affects women more often than men with a lifetime prevalence of up to 10%, has been named one of the top ten chronic physical or mental illnesses (Craske & Stein, 2016). Symptoms of this disorder typically appear in early adolescence and last into adulthood. Also, it can have an effect both on objective outcomes including missed workdays and decreased health-related quality of life (Craske & Stein, 2016). Academic underachievement, poor job performance, or even inability to work, as shown by higher unemployment rates in socially anxious individuals, are only a few of the consequences that contribute to a lower quality of life (Fink et al., 2009). It is normal to experience fear and anxiety in daily life but to be diagnosed with this type of disorder fear and anxiety must be extreme, recurrent, and related to impairments in social, occupational, or other essential areas of functioning (Craske & Stein, 2016). According to Craske and Stein (2016), if untreated, this type of disorder tends to recur chronically. A wide range of situations can cause the symptoms of SAD e.g., talking in front of an audience, getting to know someone new or someone famous, participating in social activities etc. This symptomatology can result in significant functional disability as well as academic and social dysfunction (Craske & Stein, 2016).

In SAD, individuals experience high levels of anxiety before, during, and after social circumstances. According to cognitive models (Mogg et al., 2000) individuals focus their attention on their anxiety when faced with difficult social circumstances, see themselves negatively as a social object, feel they have little control over their emotional reaction and believe their social skills are insufficient to effectively cope with different social situations Individuals also use maladaptive coping mechanisms to prevent social mishaps, such as avoidance and safety habits, accompanied by post-event rumination, resulting in a chain reaction of negative affective and physiological response which contributes to potential social apprehension (Cremers & Roelofs, 2016).

Avoidant behaviours are sometimes used by socially anxious individuals to minimize or prevent their anxiety. Avoidance behaviour, which varies from relatively mild in-situation protective behaviours e.g., preventing eye contact, to the avoidance of any physical contact outside the patient's immediate family, is also the most significant cause of disability in SAD. The sympathetic nervous system (SNS) is a distributed nervous system that affects a variety of physiological processes to mobilize threat responses. In SAD, the sympathetic nervous system is characterized by inaccurate perceptions of response to both danger and safety signals, promoting maladaptive avoidance behaviours and impairing sympathetic recovery (Evans et al., 2019)

Also, several functional imaging studies have been carried out to determine the functional correlates of patients' impaired social behaviour. According to Freitas-Ferrari et al. (2010), functional magnetic resonance imaging (fMRI) showed that some regions of the brain are hyperactive during emotional processing in SAD patients. The parahippocampal and fusiform gyrus, globus pallidus, inferior frontal gyrus, superior temporal gyrus but most constantly the amygdalae and insula were discovered to be hyperactive. The amygdala is thought to be the core component in the circuitry of fear and its activation appears to correlate with the severity of symptoms that socially anxious individuals experience. Positron emission tomography (PET) studies that show increased regional blood flow in the amygdala of patients during stressful activities including public speaking affirm the role of this area in the disorder's pathophysiology. Interestingly, with pharmacological care, this syndrome tends to be partly reversible (Fink et al., 2009).

The evidence indicates that the cause of this disorder is influenced by both individual and environmental factors. One of the individual factors that may affect this disorder is genetic. According to findings from genetic epidemiological studies, heritability levels is around 30–50 %. Specific genetic susceptibility loci Calmodulin-Lysine N-methyltransferase (CAMKMT), have been identified in genome-wide association studies of anxiety disorders. After the genetic influence, follows also some temperamental, cognitive and behavioural influences coupled with specific emotional and cerebral features. When an individual is

exposed to negative or harmful social stimuli, the amygdala and connecting fronto–striatal cortices become more activated. Environmental risk factors that can influence this disorder are familial influences, such as parental overcontrol and psychopathology, traumatic incidents in one's life, such as sexual harassment, toxic peer relationships, social factors as well as cultural influences (Pelissolo et al., 2019).

Since it was found that SAD begins in childhood and adolescence and predict subsequent psychopathology, identifying individuals at risk and intervening at an early age are critical treatment considerations. Pharmacological treatments can relieve symptoms of SAD, resulting in a significant increase in health-related quality of life and reduction in disability. An improved understanding of the neurological, cognitive, environmental, and other factors that contribute to the disorder is also needed for treatment development. With this understanding, pharmacological therapies, SSRIs in particular, can be fine-tuned to target certain mechanisms, as well as different mechanisms for different individuals (Craske & Stein, 2016). There has been a rise in interest in drug choices for the treatment of social anxiety since the late 1970s. In this thesis, I will focus on pharmacological treatments and particularly on SSRIs. A newer medication, such as SSRI, have been used more often in recent years. The Food and Drug Administration has approved paroxetine, an SSRI, as an effective treatment for individuals with a generalized social anxiety disorder (gSAD). Most SSRI trials (paroxetine, escitalopram, fluvoxamine, sertraline) appeared to show similar effectiveness as well (Rodebaugh et al., 2004).

Several measurements are widely used to assess the severity of SAD on different levels (psychosocial dysfunction, treatment response, effectiveness of therapy etc.). Liebowitz Social Anxiety Scale (LSAS) is one of those, which is the most widely used scale for measuring the severity of SAD in pharmacological trials is a 24-item clinician-administered scale that rates individuals' anxiety in a variety of social situations. Its overall score is the sum of its two subscales ("Anxiety" and "Avoidance") and ranges from 0 to 144 (Blanco et al., 2003a). Also, one rating scale called Clinical Global Impression Global Improvement score (CGI-I) measures symptom severity, treatment response and the efficacy of treatments in clinical studies. A responder was rated as very much improved (score=1) or much improved (score=2) compared to baseline (pretreatment) (Stein et al., 2003). The scale that measures the psychosocial dysfunction in three areas of life (disruption of employment, social life, and home/family life) is called the Sheehan Disability Scale (SDS). The SDS is a five-item, self-reported questionnaire that assesses how much a patient's impairment from an illness or health condition affects work/school, social life/leisure activities, and family life/home responsibilities (Stein et al., 2004). Brief Social Phobia Scale (BSPS) is a clinical rated scale that measures Fear (7 items), avoidance (7 items), and physiological arousal (4 items:

blushing, palpitations, trembling, and sweating) are all assessed on this 18-item scale (Connor et al., 2006).

This current thesis aims to examine the efficacy of pharmacological treatment, particularly SSRI in individuals with generalized social anxiety disorder in comparison with placebo (no active medication). Studying the efficacy and tolerability of different SSRIs trials (paroxetine, escitalopram, fluvoxamine, sertraline), can lead to a better understanding of different SSRIs in the treatment of gSAD and future medication improvements in this type of SAD.

Methods

Search Strategy

This study was compiled using the following databases: Web of Science and Scopus (accessed March 13, 2021). With no time limit (for a better overview of the research area), the following keywords were used:("social anxiety disorder" OR SAD) and ("selective serotonin reuptake inhibitors" OR SSRI) and (placebo). This search resulted in 215 records in total: Web of Science (n=72) and Scopus (n=127). After removing duplicates by using the program called Endnote, 192 records remained, which were then screened for reviews and irrelevance. After screening, 146 records were excluded: reviews (n = 60), wrong study design (n=31), wrong type of disorder (n=25), comparing with other treatment than SSRI (n=18), wrong population group (n= 8) and due to foreign language (n=4), resulting in 46 full-text articles to be reviewed for eligibility. After reading the full text of these papers, those that met inclusion criteria in interpreting the effectiveness of SSRI medication as a pharmacological treatment for generalized social anxiety disorder with placebo control trials were included in this systematic review. The literature search process was recorded using a PRISMA flow diagram (see Figure 1).

Inclusion & Exclusion criteria

After reading the abstract and full text, written in English, with no time limit, original published papers studies in which SSRIs have been tested for gSAD in addition to placebo were included. Also, individuals over 18 years old, males or females, who met the DSM criterion for gSAD. Exclusion criteria: review articles, meta-analysis and irrelevant studies, studies measuring treatments other than SSRI vs. placebo in the treatment of gSAD. Individuals who did not meet the DSM criterion for gSAD.

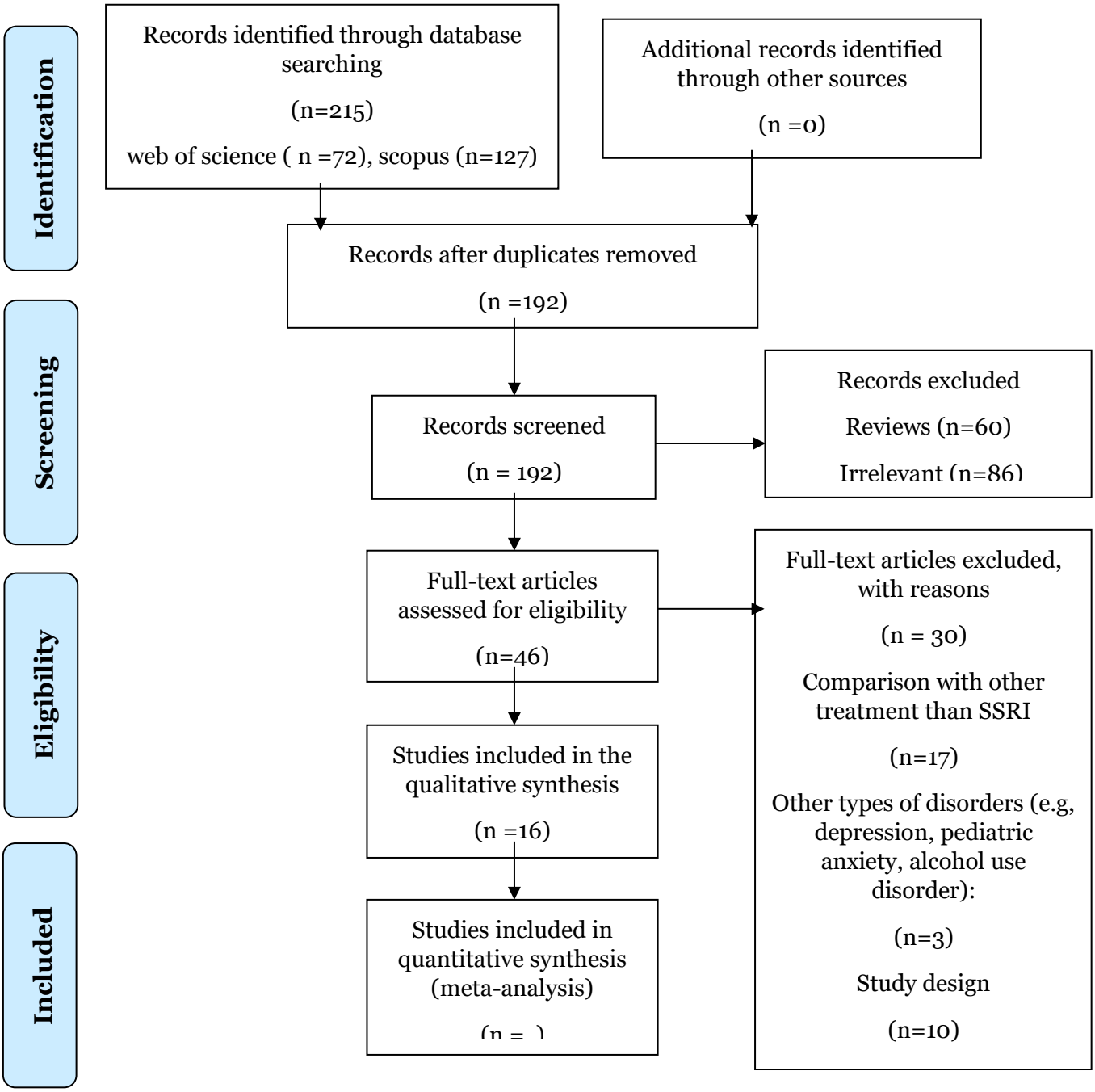
Data Extraction

The following data were included in the results section: Population: individuals who met the DSM criterion for gSAD and were over the age of 18, males or females. Intervention: selective serotonin reuptake inhibitor (SSRI) medicine. Comparison: Placebo-controlled studies where SSRIs medication (paroxetine, escitalopram, fluvoxamine, sertraline) was used

to treat individuals with gSAD. Outcome: Effectiveness of SSRI medication (measured by LSAS, CGI-I, SDS and BPSP scales) in comparison with placebo (no active medication).

Figure 1.

Prisma flow diagram



Note. Standard flow diagram used to document the literature search process. Citation: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Results

The final search resulted in 16 studies and further details about the search process can be seen in Fig. 1. The result part will be divided into five sections of SSRIs: four studies (escitalopram vs. placebo), six studies (paroxetine vs. placebo), two studies (fluvoxamine vs. placebo), one study (sertraline vs. placebo) and three studies (several SSRI, sertraline, fluvoxamine paroxetine and escitalopram vs. placebo). All the included studies in this review are summarized in Table 1 regarding information about the participants, the interventions, the comparison and the outcome from each study.

Table 1

A summary of all 16 included articles

Study	Participants	Intervention	Comparison	Outcome
Baldwin et al., 2016	Participants diagnosed with gSAD n=1615 Mean age = 36 n= males/females NA	SSRI Escitalopram (5, 10, or 20 mg/day) 12 weeks	Placebo pill	LSAS (levels of severity of SAD clinician-administered scale, rates individuals' anxiety in a variety of social situations, CGI-I (rating scale, symptom severity, treatment response and the efficacy of treatments)
Dhillon et al., 2006	Participants diagnosed with gSAD n=1000 mean age NA n=males/females NA	SSRI Escitalopram (5 ,10-20 mg/day) 12 weeks	Placebo pill	LSAS (levels of severity of SAD, clinician-administered scale, rates individuals' anxiety in a variety of social situations)
Lader et al., 2004	Participants diagnosed with gSAD. n= 839 mean age = 37 years n=males/females NA	SSRI Escitalopram (5 ,10,20 mg/day or 20 mg paroxetine) 24 weeks	Placebo pill	LSAS (levels of severity of SAD, clinician-administered scale, rates individuals' anxiety in a variety of social situations) CGI-I (rating scale, symptom severity, treatment response and the efficacy of treatments SDS (five-item, self-reported questionnaire assesses psychosocial dysfunction in three areas of life (disruption of employment, social life, and home/family life)
Stein et al., 2004	Participants diagnosed with gSAD n= 1,197 mean age NA n=males/females NA	SSRI Escitalopram (5, 10, or 20 mg/day) 12 weeks	Placebo pill	LSAS factorial structure, which measures six factors linked to various aspects of disability (factor 1: social interaction; factor 2: eating and drinking in public; factor 3: speaking in public; factor 4: assertiveness; factors 5: observation fear and factor 6: partying).
Allgulander, C. (1999).	Participants diagnosed with gSAD n=92	SSRI paroxetine 20-50 mg/day 12 weeks	Placebo pill	LSAS (the levels of severity of SAD, clinician-administered

	mean age=41 n=48 males n=44 females			scale, rates individuals' anxiety in a variety of social situations) CGI-I (rating scale, symptom severity, treatment response and the efficacy of treatments)
Baldwin, D. S. (2000)	Participants diagnosed with gSAD n=862 mean age NA n=males/females NA	SSRI Paroxetine (20 ,40 60 mg/day) 12weeks	Placebo pill	LSAS (the levels of severity of SAD, clinician-administered scale, rates individuals' anxiety in a variety of social situations) CGI-I (rating scale, symptom severity, treatment response and the efficacy of treatments SDS (five-item, self-reported questionnaire assesses psychosocial dysfunction in three areas of life (disruption of employment, social life, and home/family life)
Blanco et al., 2003a	Participants diagnosed with gSAD n=182 mean age NA n=males/females NA	SSRI Paroxetine 20-50 mg/day 12 weeks	Placebo pill	LSAS (levels of severity of SAD clinician-administered scale, rates individuals' anxiety in a variety of social situations)
Lydiard and Bobes, (2000)	Participants diagnosed with gSAD n= of 861 mean age =36 n=males/females NA	SSRI Paroxetine flexible-dose of (20–50 mg/day) fixed dose (20, 40, or 60 mg/day) 12 weeks	Placebo pill	LSAS (levels of severity of SAD clinician-administered scale, rates individuals' anxiety in a variety of social situations) CGI-I (rating scale, symptom severity, treatment response and the efficacy of treatments
Stein et al., 1998	Participants diagnosed with gSAD n=187 mean age=36 n=81 males n=106 females	SSRI Paroxetine 20-50 mg/day 12 weeks	Placebo pill	LSAS (levels of severity of SAD clinician-administered scale, rates individuals' anxiety in a variety of social situations) CGI-I (rating scale, symptom severity, treatment response and the efficacy of treatments
Stein et al., 2001	Participants diagnosed with gSAD n=829 mean age=36 n=males/females NA	SSRI Paroxetine (20–50 mg/day) 12 weeks	Placebo pill	LSAS (levels of severity of SAD clinician-administered scale, rates individuals' anxiety in a variety of social situations) CGI-I (rating scale, symptom severity, treatment response and the efficacy of treatments
Stein et al., 1999	Participants diagnosed with gSAD n=92 mean age=39 n=males/females NA	SSRI Fluvoxamine (50mg/day) 12 weeks	Placebo pill	LSAS (levels of severity of SAD clinician-administered scale, rates individuals' anxiety in a variety of social situations)

				CGI-I (rating scale, symptom severity, treatment response and the efficacy of treatments SDS (five-item, self-reported questionnaire assesses psychosocial dysfunction in three areas of life (disruption of employment, social life, and home/family life)
Stein et al., 2003	Participants diagnosed with gSAD n= (112) mean age=36 n=58 males n=53 females	SSRI Fluvoxamine (100–300 mg/day) 12-24 weeks	Placebo pill	LSAS (levels of severity of SAD clinician-administered scale, rates individuals' anxiety in a variety of social situations) CGI-I (rating scale, symptom severity, treatment response and the efficacy of treatments)
Connor et al., 2006	Participants diagnosed with gSAD n=345 mean age=35 n=males/females NA	SSRI Sertraline, (50–200 mg/day) 12 weeks	Placebo pill	BSPS (clinical rated scale assesses fear, avoidance and physiological arousal)
Blanco et al., 2003b	Participants diagnosed with gSAD n=896 mean age NA n=males/females NA	SSRI (paroxetine, fluvoxamine, sertraline) Not reported dosage 12 weeks	Placebo pill	LSAS (levels of severity of SAD clinician-administered scale, rates individuals' anxiety in a variety of social situations) CGI-I (rating scale, symptom severity, treatment response and the efficacy of treatments)
Mayo-Wilson et al., 2014	Participants diagnosed with gSAD n= 3159 mean age = 36 n=males/females NA	SSRI (paroxetine, escitalopram, fluvoxamine, sertraline) Not reported dosage 12 weeks	Placebo pill	LSAS (levels of severity of SAD clinician-administered scale, rates individuals' anxiety in a variety of social situations) CGI-I (rating scale, symptom severity, treatment response and the efficacy of treatments)
Van der Linden et al., 2000	Participants diagnosed with gSAD n=61 mean age NA n=males/females NA	SSRI(fluvoxamine, sertraline , 50-200 mg/day Paroxetine 10-50mg/day) 12 weeks	Placebo pill	LSAS (levels of severity of SAD, clinician-administered scale, rates individuals' anxiety in a variety of social situations) CGI-I (rating scale, symptom severity, treatment response and the efficacy of treatments)

Note. NA= no available

Escitalopram vs. Placebo

Four studies (Baldwin et al., 2016; Dhillon et al., 2006; Lader et al., 2004; Stein et al., 2004) compared the efficacy of SSRIs (escitalopram) with placebo. In the study by Baldwin et al. (2016), participants were diagnosed with gSAD, (n=1598), mean age 36, with equal

distribution of men (44.8%) and women (55.2%) (without exactly provided number of men/females). Researchers used LSAS, which is the most used primary efficacy scale in medication studies of SAD, to measure the short-term efficacy of an SSRI escitalopram (5, 10 and 20 mg/day) in comparison with placebo. In 12 weeks, researchers calculated the treatment difference in the LSAS total score. At all doses (escitalopram 5 mg, 10 mg, 20 mg/day and 10–20 mg/day), the overall difference in treatment effect was in favour of escitalopram versus placebo.

In the study (Dhillon et al., 2006) researchers compared the short- and long-term effectiveness of escitalopram (5,10,20 mg/day) with placebo in participants (n=1000) diagnosed with gSAD over 12 and 24 weeks. This study did not report participants mean age or a total number of males/females in the study as the previous study did (Baldwin et al., 20016). Researchers used the LSAS scale to measure the effectiveness of escitalopram with a placebo. From week 2 onwards, the mean reduction in LSAS scores from baseline was substantially larger with escitalopram 5 and 20 mg/day compared to placebo, and with escitalopram 10 mg/day compared to placebo from week 4 onwards. Furthermore, in the researchers' relapse-prevention study, escitalopram patients had a considerably longer time to relapse and a lower risk of relapse than placebo patients, and escitalopram patients relapsed less frequently than placebo patients. In a subgroup of patients from the relapse-prevention research, escitalopram was also linked to a higher mental health-related quality of life than placebo.

Lader et al. (2004) compared the effectiveness and tolerability of escitalopram to placebo in the short- and long-term treatment of participant with gSAD over 24 weeks of the period. Participants (n=839), with mean age 37, diagnosed with gSAD were selected for this study. Similar with previous study (Dhillon et al., 2006) this study also did not report a total number of males and females. The findings of this study revealed that all escitalopram doses (5, 10, and 20 mg) are effective and well-tolerated in the short- and long-term treatment of gSAD. Also, all three doses of escitalopram as shown to be significantly more effective than placebo at the end of the 24 weeks on both the primary LSAS and secondary efficacy parameters CGI-I and SDS. In terms of lowering the mean LSAS total ratings, escitalopram was substantially more successful than placebo. Based on the change from baseline in LSAS mean score, the analysis also found that the 20 mg dose of escitalopram was significantly superior to the 20 mg dose of paroxetine. Furthermore, from week 2 onwards, the mean reduction in LSAS total scores from baseline was substantially greater with escitalopram 5 and 20 mg/day than placebo, and with escitalopram 10 mg/day from week 4 onwards. Also in this study, it was seen that escitalopram recipients had a longer time to relapse and a lower risk of relapse than placebo recipients in a 24-week, and substantially fewer escitalopram than placebo recipients relapsed.

Stein et al. (2004) researched the short-term effectiveness of escitalopram (5, 10, or 20 mg/day) vs. placebo across different subgroups of participants by using LSAS over 12 weeks. In this study participants (n=1.197) were diagnosed with gSAD. This study did not report the mean age or number of males/females participants that participated in the study. Stein et al. (2004) used the LSAS factorial structure (see Table 1), which examines six factors linked to various aspects of disability (factor 1: social interaction; factor 2: eating and drinking in public; factor 3: speaking in public; factor 4: assertiveness; factors 5: observation fear and factor 6: partying). The LSAS factor analysis showed escitalopram was significantly superior to placebo for all six symptom dimensions. Results from this study also showed that escitalopram was successful in both younger and older patients, male and female patients, and patients with more and less serious social anxiety symptoms also patients with and without comorbid depressive symptoms.

Paroxetine vs. Placebo

Six studies (Allgulander, 1999; Baldwin, 2000; Blanco et al., 2003a; Lydiard & Bobes, 2000; Stein et al., 1998; Stein et al., 2001) compared the efficacy of an SSRI (paroxetine) to placebo.

The study by Allgulander (1999) contrasted the short-term effectiveness of paroxetine (20-50 mg/day) with placebo in participants (n=92) with gSAD in terms of relieving anxiety symptoms and improving phobic avoidance over 12 weeks of the period. Participants had a mean age of 41 and the total number of males was 44 and females 48. Researchers used LSAS, CGI-I scales to measure the effectiveness of paroxetine in comparison with placebo. The difference in overall LSAS score was significant from week 4 onwards, and CGI-I indicated a significant difference between the treatment groups as well, starting after 4 weeks. This study also revealed that paroxetine was more successful than placebo in relieving anxiety symptoms, as shown by the fact that two of the paroxetine participants reported dating and forming romantic relationships for the first time. Also, small children's parents reported having more patience with them. Some people taking paroxetine were looking for new jobs or dealing with social relationships or other issues that they had been putting off for a long time.

In the study (Baldwin, 2000) researcher compared the short-term effectiveness of paroxetine (20, 40,60 mg/day) with placebo in participants (n=862) diagnosed with gSAD over 12 weeks of the period. This study did not report participants mean age or number of males/females as previous study (Allgulander, 1999). To examine the efficacy of paroxetine vs. placebo, researchers employed the following measurements: SDS, LSAS, and CGI-I. The total LSAS score was considerably lower in paroxetine-treated participants compared to placebo, and the percentage of responders on CGI-I was significantly greater after 4 weeks in paroxetine-treated participants compared to placebo, and this remained throughout the 12-

week experiment. On the SDS scale, there was a significant advantage for participants taking paroxetine over placebo in all three domains (work, social life and family life). According to the findings of (Baldwin, 2000), paroxetine was successful in reducing both depressive symptoms as well as disability and impairment in participants with gSAD. That can assist individuals with gSAD in taking on daily challenges, hobbies, and occupations that their fear and anxiety previously prevented them from doing.

Blanco et al. (2003a) studied the short-term effectiveness of either a placebo or a flexible dose of the SSRI paroxetine (20-50 mg) in gSAD participants (n=182), over 12 weeks. Similar to a previous study by (Baldwin, 2000), this study also did not report the participants mean age or the total number of males/females participants. To assess the efficacy of paroxetine vs. placebo, researchers used LSAS. The difference in total LSAS scores was 30.5 points for paroxetine vs. 14.5 points for placebo, indicating a highly significant difference. The placebo-treated patients experienced a slight reduction in SAD symptoms, while the paroxetine-treated patients experienced a gradual decrease in symptoms that became substantial after two weeks. The possibility of relapse has also been investigated. Responders were randomized to 12 weeks of treatment with paroxetine or placebo. Of paroxetine-treated participants, 13% relapsed as opposed to 63% of those on placebo.

In the study (Lydiard & Bobes, 2000) researchers compared the short-term effectiveness of paroxetine (flexible-dose 20-50mg/day and fixed-dose 20,40 or 60 mg/day) or placebo in treating the participants diagnosed with gSAD (n= 861, mean age 36) over 12 weeks of the period. This study did not report a total number of females/males participants. Lydiard and Bobes (2000) used LSAS and CGI-I scales for the comparison of efficacy between paroxetine and placebo. All statistical tests comparing paroxetine with placebo (LSAS and CGS-I) showed that paroxetine is effective and well-tolerated medication in comparison with placebo. The average reduction in LSAS scores from baseline was higher in paroxetine-treated participants than in the placebo, indicating that paroxetine improved social anxiety symptoms more than placebo-treated patients. By week 4 flexible-dose studies, paroxetine-treated patients had considerably better LSAS score ratings than placebo receivers, and this continued through all subsequent evaluations to the endpoint (week 12). According to Lydiard and Bobes (2000), a more robust response was seen in the flexible-dose studies than in the fixed-dose studies. It is possible that some patients required higher or lower doses than the fixed-dose design allowed. Person optimization was not feasible in this study since all participants were dedicated to a single dosage. Additionally, no further progress in efficacy in the high-dose (60 mg/day) group indicates that for most patients there is no improvement in prescribing doses higher than 50 mg/day. Based on the accrued evidence, a starting dose of 20 mg/day is recommended according to this study.

Stein et al. (1998) compared the short-term effectiveness of paroxetine, with participants diagnosed with gSAD,(n=187) versus placebo over 12 weeks of the period. The total number of males participating in this study was 81 and females 106, with a mean age of 36. The initial dose was 20 mg of paroxetine or placebo, with a weekly increase of 10 mg (maximum 50 mg). Researchers used LSAS and CGI-I scales to measure the effectiveness of paroxetine in comparison with placebo. Beginning at week 4 and going to week 12, the efficacy of paroxetine was significantly greater than placebo showed by CGI-I (improvement score 1-2). Also, the mean reduction on the LSAS scale total scores was higher in paroxetine treated participants than in placebo.

Stein et al. (2001) compared the short-term effectiveness of paroxetine (20-50mg/day) with a placebo over 12 weeks period. Participants (n=829) were diagnosed with gSAD with a mean age of 36 years. The total number of males participating in this study was 415 and females 414. Researchers from this study used measurements LSAS and CGI-I to assess the effectiveness of paroxetine in comparison with placebo. According to study results, the effect of the baseline score was statistically significant in favour of paroxetine in comparison with placebo.

Fluvoxamine vs. Placebo

Two studies (Stein et al., 1999; Stein et al., 2003) compared the efficacy of SSRI (fluvoxamine) with placebo. In the research by Stein et al. (1999), a substantial difference between fluvoxamine (50mg/day) and placebo was observed, when comparing the short-term effects of these two treatments. Participants (n=92, mean age 39) with gSAD were treated with the fluvoxamine in 12 weeks. The total number of males/females was not reported by this study. Efficacy between fluvoxamine and placebo was assessed by the following scales: LSAS, CGI-I and SDS. Participants' CGI-I progress ratings were much or very much increased by the end of the study relative to pre-treatment. The LSAS scores followed a similar pattern of response, with fluvoxamine statistically differing from placebo at the 6-week and beyond time points. On two of the three subscales of the SDS, fluvoxamine outperformed placebo, resulting in substantial improvements in work and family life and home functioning but only a trend toward improved social life functioning. The study also revealed several side effects: nausea and insomnia were the two most common side effects that led to fluvoxamine discontinuation in the fluvoxamine group. Dizziness, diminished libido, nervousness, and somnolence were other treatment-emergent signs and symptoms for which fluvoxamine outperformed placebo by at least 10%.

The study Stein et al. (2003) compared the short- and long-term effectiveness of fluvoxamine (100–300 mg/day) to placebo over 12 and 24 weeks. Participants (n=112, mean age 36) were diagnosed with gSAD. The total number of males was 58 and females 53. Researchers in this study used LSAS and CGI-I to compare the effectiveness of fluvoxamine

versus placebo. At week 12 in the acute phase and week 24 in the extension phase, the fluvoxamine group showed efficacy in terms of lowering LSAS total scores when compared to the placebo group. The percentage of responders (defined as much improved on the CGI-I) was statistically higher in the fluvoxamine group (38%) than in the placebo group (28%). The current data indicate that, in comparison to the placebo group, subjects on fluvoxamine tended to progress during maintenance care from weeks 12 to 24. Relapse prevention trials, in which drug responders are randomized to either ongoing therapy or a placebo, have been used to determine whether a treatment has a higher long-term success rate than a placebo. The current findings are consistent with previous research showing that SSRIs can prevent relapse in the long-term treatment of gSAD.

Sertraline vs. Placebo

In the study by Connor et al. (2006), the short-term effectiveness of the SSRI sertraline was compared to placebo over 12 weeks. In this study, participants (n=345, mean age 35) were diagnosed with gSAD. The total number of males/females participating in this study was not reported. The efficacy of sertraline versus placebo was assessed by BSPS. Treatment with sertraline resulted in a substantial decrease in the mean overall BSPS score in the entire study (significant reduction in fear, avoidance, and physiological arousal, especially blushing and palpitations) when compared to placebo. The relationship between the three core symptom domains of gSAD (fear, avoidance, and physiological symptoms), as well as the impact of treatment on each, has received relatively little attention in research studies. According to the study, sertraline outperformed placebo on all three SAD clinical domains, as well as on two of the individual physiological products (blushing and palpitations)

Several SSRIs (fluvoxamine, paroxetine sertraline escitalopram) vs. Placebo

Tre studies (Blanco et al., 2003b; Mayo-Wilson et al., 2014; Van der Linden et al., 2000) compared the efficacy of several SSRI medication (fluvoxamine, paroxetine sertraline escitalopram) with placebo. Blanco et al. (2003b) compared the short-term effectiveness of multiple SSRI (paroxetine, fluvoxamine, sertraline) medications to placebo over 12 weeks of the period. The participants (n=896) were diagnosed with gSAD. The study did not report the mean age or the total number of males/females. Also, this study also did not report the exact dosage of SSRI medication (paroxetine, fluvoxamine, sertraline). The efficacy of this SSRI medication was assessed by LSAS and CGI-I. The result shows that paroxetine, fluvoxamine, sertraline were significantly superior to placebo. According to this study, there are several reasons to recommend SSRIs as a first-line treatment for SAD: they are generally well-tolerated, easy to dose, and relatively safe in overdose; they are effective in other anxiety disorders and depression, which are frequently comorbid with SAD. Finally, SSRIs were the first antidepressants to reliably cross the Lan–DeMets lines, giving the effect size an extra

measure of authenticity and stability, as well as providing an objective explanation for the standard clinical practice of using SSRIs as first-line treatment for SAD.

In the study, Mayo-Wilson et al. (2014) researchers compared the short-term effectiveness of SSRI medication (fluvoxamine, paroxetine sertraline escitalopram) over 12 weeks period. Participants (n=3159) was diagnosed with gSAD , with a mean age of 36 years. The study did not report the total number of males/females participating in the study. Similar with previous study (Blanco et al., 2003b), this study also did not report the exact dosage of SSRI medication (fluvoxamine, paroxetine sertraline escitalopram). Efficacy was assessed by using LSAS. Results showed that several SSRIs drugs (escitalopram fluvoxamine, paroxetine, sertraline) have greater efficacy compared with placebo. There was also a discussion in this study about the variations in tolerability and side-effects of these SSRI medications, which are especially significant in the treatment decision. Some SSRIs, such as paroxetine, have the highest risk of discontinuation effects, both during and after treatment. Also, some side effects like increased agitation and sexual dysfunction can be particularly distressing for people with gSAD, especially if these effects are unexpected or if they reinforce established concerns.

Van der Linden et al. (2000) compared the short-term effectiveness of several SSRI medication as well (paroxetine, sertraline and fluvoxamine) with placebo. In this study, researchers did not report participants mean age or the total number of males/females. Participants (n=30), diagnosed with gSAD, were recruited and treated with fluvoxamine (150 mg/day) vs. placebo over 12 weeks. Efficacy of fluvoxamine versus placebo was assessed by LSAS, CGI-I and SDS. There was seen a significant reduction in LSAS in favour of the fluvoxamine group. Also, response rates on CGI-I, was 43 % on the fluvoxamine group and 23 % on the placebo group (response defined as much improved or very much improved on CGI-I). Fluvoxamine treatment also resulted in a significant decrease in psychosocial disability as measured by the SDS. Participants (n=12) were recruited and treated with sertraline (50-200 mg/day) over 10 weeks. The efficacy of sertraline versus placebo was assessed by CGI-I. Six participants on sertraline and one on placebo were rated as much improved or very much improved on CGI-I). Participants (n=36) diagnosed with gSAD were also recruited in this study and treated with paroxetine (10-50mg/day) over 12 weeks. The efficacy of paroxetine versus placebo was assessed by CGI-I. The result showed that 30 responders were rated as much improved or very much improved on CGI-I.

Discussion

This study aimed to compare the effectiveness of pharmacological therapy, specifically SSRI with placebo, in individuals with gSAD. The main finding in this systematic review is that SSRI consistently demonstrated greater efficacy compared to placebo, as

assessed by the LSAS, CGI-I, SDS and BPSP on a series of endpoint comparisons involving a change in scores from baseline and response rates.

Results from four studies (Baldwin et al., 2016; Dhillon et al., 2006; Lader et al., 2004; Stein et al., 2004) have shown that escitalopram was effective and well-tolerated in the short- and long-term treatment of SAD, also that escitalopram was successful in both younger and older patients, male and female patients, and patients with more and less serious social anxiety symptoms. There was little evidence of differential efficacy within or between classes of drugs. The only evidence was seen from the one study (Lader et al., 2004) who found that the 20 mg dose of escitalopram was significantly superior to the 20 mg dose of paroxetine. There was much difference in tolerability on the other side which can be also important in the choice of treatment. Some side effects such as increased agitation and sexual dysfunction can be especially distressing for individuals with gSAD. In the study, Stein et al. (1999) several side effects nausea and insomnia were the two most common side effects that led to fluvoxamine discontinuation in the fluvoxamine group. Other treatment-emergent signs and symptoms for which fluvoxamine outperformed placebo by at least 10% were dizziness, reduced libido, nervousness, and somnolence.

At present, there is more evidence of the efficacy of paroxetine for gSAD than for any other SSRI as it was shown by six studies comparing paroxetine and placebo presented in the result section (Allgulander, 1999; Baldwin, 2000; Blanco et al., 2003a; Lydiard & Bobes, 2000; Stein et al., 1998; Stein et al., 2001). Also, there was a lot of benefit from taking the paroxetine according to participants such as dating and forming romantic relationships for the first time, looking for new jobs, or dealing with social relationships or other issues that they had been putting off for a long time.

Results from two studies (Stein et al., 1999; Stein et al., 2003) showed that escitalopram has greater efficacy when compared with placebo both in short- and long-term period. According to Stein et al. (2003) fluvoxamine subjects continued to improve during maintenance treatment from weeks 12 to 24 as compared to the placebo community. During the extension process of the current study, both social anxiety symptoms and related impairment improved in the medication-treated community. Also, it was shown that SSRIs can prevent relapse in the long-term treatment of SAD. Several concerns about how to best treat SAD, in the long run, remain unanswered. These include concerns about how to better support patient adherence in chronic conditions, the best sequencing and combination of pharmacotherapy and psychotherapy, and when medication should be stopped.

A study (Connor et al., 2006) found that sertraline was more effective in a short-term period than a placebo. The relationship among three key clinical dimensions of SAD (fear, avoidance, and physiological anxiety symptoms), and the effect of treatment on each other

assessed by BSPS appear to be more correlated with avoidance behaviours which are sometimes used by individuals with SAD to minimize or prevent their anxiety.

Tre studies (Blanco et al., 2003b; Mayo-Wilson et al., 2014; Van der Linden et al., 2000) showed that several SSRIs drugs (escitalopram fluvoxamine, paroxetine, sertraline) have greater efficacy compared with pill placebo. But there was also a discussion about the variations in tolerability and side-effects of these SSRI medications, which are especially significant in the treatment decision. Pharmacotherapy should be chosen based on effectiveness, as well as potential side effects, contraindications, and interactions.

Limitations

There are a few limitations of this systematic review that need to be mentioned. The search process was not assessed by a second opinion (just the author of this study assessed the search process). Also, the included studies all evaluated different endpoints, it was difficult to compare and obtain sufficient results for the various periods due to the limited number of studies. Further, the choice of the search string and studies selection were both based on the author's experience and knowledge. Some limitations coupled with studies are that some research gave more extensive information about participants (mean age or the total number of males/females), while others only addressed these things briefly. Also, some studies (Blanco et al., 2003b; Mayo-Wilson et al., 2014) did not provide the actual dosage of SSRI medication, which can reduce the study's validity by not knowing which dosage can help individuals improve their condition.

Future Research

Future research would undoubtedly shed more light on the complexities of SAD. Thorough characterization of symptom subtypes and medical comorbidity may already help predict response to pharmacotherapy in SAD. The findings indicate that making a strict distinction between patients who fear most social situations and those who do not is ineffective when deciding whether to use an SSRI. Another thing to consider is whether SAD is coexisting with other psychological conditions. However, up to 80% of SAD patients can have a comorbid condition, the most common of which are obsessive-compulsive disorder (OCD), severe depression, panic disorder, and alcohol and substance abuse. It can be useful that a medication used to treat SAD patients could also have a beneficial effect on any comorbid conditions (Baldwin, 2000).

Ethical and Societal Aspects

Only studies with participants over the age of 18 were included in this systematic review, as well as those with voluntary participation and signed informed consent before the start of the research project. In the studies, no one was harmed during the research procedure. Therefore, there are no ethical issues with the research. Individuals with gSAD exhibit distressing/disabling social concerns in many social situations. As a result, it can have

an impact on a variety of facets of life, including social, familial, and professional ones (no ability to work). All inabilities that individuals with gSAd experience can have a great impact on society in terms of increased economic cost. Further, given the incidence and severity of impairment caused by SAD, it is obvious that knowing the right diagnosis and treatment is essential for public health (Blanco et al., 2003b).

Conclusion

In conclusion, all the 16 articles included in this systematic review showed that SSRI medication was significantly superior in comparison with placebo. SSRI medication was shown to be effective and well-tolerated both in short- and long-term period, successful in reducing both anxiety symptoms as well as disability and impairment in people with gSAD. Furthermore, it was shown that SSRIs can prevent relapse in the long-term treatment of SAD and had a beneficial effect on different areas of individuals lives such as work, performance, romantic relationships etc.

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