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REVIEW ARTICLE

Antidepressants for social anxiety disorder: A systematic review and meta-analysis

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Abstract

Aim: This systematic review is aimed to update and reintegrate the pharmacotherapy of social anxiety disorder (SAD), including the Japanese medical database.

Methods: We conducted a systematic review and meta-analysis of pharmacotherapy of SAD according to the Medical Information Distribution Service. We used data from a most recent systematic review, and updated search were conducted using MEDLINE, PubMed, CENTRAL, ICTRP, and ICHUSHI from August 1st, 2017 to January 31st, 2022. The outcome were response rates assessed by Clinical Global Impressions Improvement, efficacy assessed by the Liebowitz Social Anxiety Scale (LSAS), and dropout rates. We performed a random effect of meta-analysis to obtain the differences in each outcome between active medication and placebo. We used RevMan version 5.3 for analyses.

Results: We identified 5 studies through update search and performed meta-analysis for 33 studies on selective serotonin reuptake inhibitor (SSRI) and 6 studies on serotonin noradrenalin reuptake inhibitor (SNRI). The response rate (RR = 1.62) and the LSAS score reduction (mean difference = −9.65) of SSRI, and the response rate (RR = 1.57) and the LSAS score reduction (mean difference = −11.72) of SNRI were significantly different from placebo. The dropout rates of SSRI or SNRI were not significant. The response rates of SSRIs in both Japanese studies (RR = 1.44) and countries other than Japan (RR = 1.67) were significant. Most findings were based on low quality of evidence.

Conclusion: SSRIs are valid option for pharmacotherapy of SAD including Japanese patients. SNRIs are another effective option. However, the results should be interpreted cautiously due to several risk of bias.

KEYWORDS
antidepressants, Japan, meta-analysis, social anxiety disorder, systematic review

1 | INTRODUCTION

In Japan, the lack of evidence-based guidelines for the treatment of anxiety has been a recognized clinical problem, and the need for new guidelines has been pointed out. In this context, the Japanese Society of Neuropsychopharmacology and the Japanese Society of Anxiety and Related Disorders decided to jointly develop guidelines for the treatment of Anxiety Disorders in accordance with the Medical Information Distribution Service (Minds). This study was conducted as part of this project and will serve as the basis for the development of guidelines for the pharmacotherapy of social anxiety disorder (SAD).

SAD has traditionally been known as "Taijin Kyofusho (TKS)" among Japanese psychiatrists, which is stated in the glossary of the cultural concept of distress in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5).[1] TKS has a unique characteristic in that patients with TKS avoid social situations because they are afraid that their presence could offense to others or make others feel uncomfortable.[2] Although SAD in Japan has a unique context comparing to other countries, the 12-month prevalence of SAD in Japan was reported 0.8%,[3] which was lower than those of 8% in the United States[4] or those of 2%–5% in Europe.[5] However, the prevalence of SAD in Japan could have been underestimated due to low response rate (55%) for the survey; presumably, it is not recognized as a treatable diseases.[3] Moreover, a nation-wide survey in the United States revealed that only 35% patients with SAD received specific treatments for SAD.[6] In light of these facts, there is a need for a better understanding of SAD and consideration of appropriate strategies to control it.

Regarding the treatment of SAD, currently existing systematic reviews include a network meta-analysis on psychotherapy and pharmacotherapy,[7] systematic review on pharmacotherapy,[8] and the latest network meta-analysis on pharmacotherapy.[9] Focusing on the pharmacotherapy, the efficacy, and high acceptability of selective serotonin reuptake inhibitor (SSRI) for SAD have been reported in these previous reviews. In addition to SSRIs, RCTs with the serotonin noradrenalin reuptake inhibitor (SNRI), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase A (RIMAs), anticonvulsants with gamma-amino butyric acid (GABA) analogues, benzodiazepines, the antipsychotics, and the noradrenergic and specific serotonergic antidepressant (NaSSA) have been reported, which could be effective treatment options, but the number of trials is small and the quality of evidence was reported to be low.[8]

Although there are systematic reviews on the pharmacotherapy of SAD as described above, there are no reports on differences in drug responsiveness in populations with different cultural backgrounds. SAD is a disease with culturally bonding characteristics, and it is necessary to confirm whether there are also differences in the responsiveness to pharmacotherapy between, for example, Western and Asian populations. Especially in Japan, where SAD was known as TKS before the diagnostic criteria for SAD were established, it is presumed that the efficacy of pharmacotherapy for SAD could be different.

The aim of this study is to conduct a systematic review on the pharmacotherapy for Japanese patients with SAD. The previous systematic reviews, both the Cochrane review[8] and the network meta-analysis,[9] did not include a Japanese medical database such as ICHUSHI. Hence, we have conducted a new systematic review, and this differentiates our review from the others. This is the first systematic review to include a Japanese database and to examine the efficacy of Japanese patients with SAD on pharmacotherapy.

2 | METHODS

2.1 | Literature search

This systematic review and meta-analysis are conducted as a part of making a clinical practice guideline for anxiety disorder in Japan according to the procedure proposed by Minds.[10] The clinical question is what the most recommended medications for adult patients with social anxiety disorder is. Inclusion criteria for present systematic review are based on the patients, intervention, comparison, and outcomes according to PICO framework: (1) The patients are adult patients with social anxiety disorder according to the DSM-IV, the DSM-IV-TR, and the DSM-5. We excluded studies included some patients who were under 18 years old. (2) The intervention and comparison are any pharmacotherapy and placebo. The study design must be randomized control trials. The interventions are using SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), SNRIs (eg, venlafaxine), NaSSAs (eg, mirtazapine), 5HT1A partial agonists (eg, buspirone), Anticonvulsants (eg, gabapentine and pregabaline), Antipsychotics (eg, olanzapine), Benzodiazepines (eg, clonazepam and bromazepam), Beta-blockers (eg, atenolol), MAOIs (phelelzine), Noradrenaline reuptake inhibitors (NARIs; atomoxetine), RIMAs (brofaromine and moclobemide), Serotonin antagonist and reuptake inhibitors (SARIs; nefazodone), and other medications (eg, vortioxetine, vilazodone). (3) The primary outcomes are short-term response rates, a short-term efficacy of pharmacotherapy, and short-term dropout rates for any reason. Additionally, the studies must be already published, or unpublished but registered in International Clinical Trials Registry Platform (ICTRP). Also, we included original articles written in English or Japanese.

In this process, we identified a most recent systematic review[8] through PubMed and CENTRAL. We used data from this previous systematic review, and updated search were conducted by NM and YF using MEDLINE, PubMed, CENTRAL, and ICTRP from August 1st, 2017 to April 30th, 2018. We added a Japanese database ICHUSHI which was not included in the previous systematic review, and the search period was until April 2018. The terms used in this review were shown in Table S1. Additionally, the reviewers (NM and HI) conducted an updated search on February 1, 2022, for studies published between May 1, 2018 and January 31, 2022.

2.2 | Screening

Two independent reviewers (NM and YF) performed the 1st screening assessing title and abstract of included articles. Then,

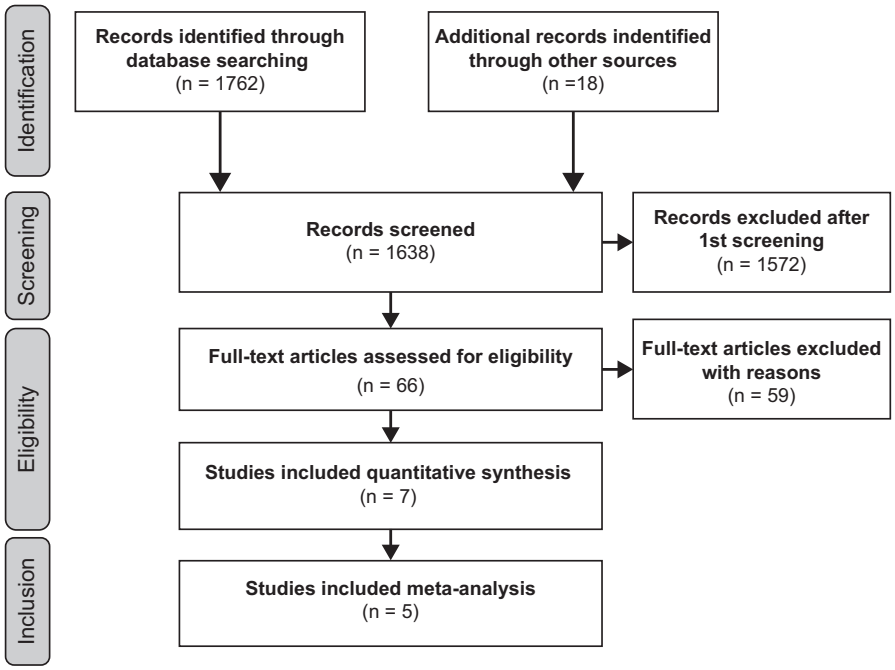

FIGURE 1 PRISMA diagram of study selection flow

two independent reviewers (NM and HI) performed the 2nd screening assessing full text of the articles extracted by 1st screening.

2.3 | Outcomes

Three outcomes were selected to evaluate the balance between benefits and harms. The primary outcome of this study was response rates for a pharmacotherapy assessed by Clinical Global Impressions Improvement scale (CGI-I). The CGI-I ranges from 1 (normal, not at all ill) to 7 (the most extremely ill). The response was defined as having an improvement of item score of 1 or 2. The secondary outcome was an efficacy of pharmacotherapy. The efficacy was defined by the reduction in SAD symptom severity assessed by the Liebowitz Social Anxiety Scale (LSAS). The LSAS is a 24-item scale that assess both fear and avoidance in social situations. The severity of SAD symptoms using the LSAS could be divided into moderate social phobia (55–65), marked social phobia (65–80), and severe social phobia (80–95). The third outcome was a dropout rate. Dropout, including reasons other than side effects, was defined as the outcome of this study.

2.4 | Risk of bias assessment

We used the Cochran tool for assessing risk of bias, and included studies were scored "low risk," "high risk," or "unclear" on the selection bias (randomization and allocation concealment), the performance bias or the detection bias (blinding of patients and researchers), the attrition bias (intention to treat and incomplete outcome data), and the other bias.

2.5 | Quality of evidence

Quality of Evidence for each outcome was evaluated according to the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) guideline. The strength and importance of the evidence was assessed for each of the outcomes of response rate, and dropout rate, and a total body of evidence was generated.

2.6 | Data analysis

We performed a random effect of meta-analysis to obtain the differences in response rate, efficacy, and dropout rate between active medication and placebo. We used a risk ratio (RR) and 95% confidence interval (CI) for dichotomous outcomes, and a standardized mean difference for continuous outcomes. The I^2 were reported as measures for heterogeneity between studies. I^2 reflects observed heterogeneity in percentages, with 0% indicating no heterogeneity and 25%, 50%, and 75% considered to be low, medium, and high levels of heterogeneity. We visually inspected for publication bias from funnel plot for response rates, efficacy, and dropout rates.

3 | RESULTS

3.1 | Study selection

The initial database search identified 1762 studies published between August 1st, 2017 and April 30th, 2018 (PubMed = 547, MEDLINE = 467, CENTRAL = 453, ICTRP = 19, ICHUSHI = 276). Eighteen additional studies were added, which were detected through previous systematic review.[8] Total identified studies were

1780, and 142 duplicates were removed. After screening the titles and abstracts of the 1638 studies, the full-text versions of a total of 66 studies were reviewed. Second screening excluded 59 studies and detected seven eligible studies. All of them investigated the effect of pharmacotherapy for SAD; however, two studies were excluded. One study was excluded because the full text was unavailable in English or Japanese, and the other (NCT00182533) because the results have not been published yet. Finally, five studies (SSRI 2 (paroxetine[11] 1, escitalopram[12] 1), SNRI 1 (desvenlafaxine 1), vortioxetine[13] 1, vilazodone[14] one were identified, which can be included to the analysis (Figure 1). The previous systematic review[8] included 31 studies for SSRI, five studies for SNRI, no study for Vortioxetine, and no study for Vilazodone. Eventually, we performed meta-analysis for 36 studies (30 studies on SSRI, four studies on SNRI, and two studies on both SSRI and SNRI).

An updated search conducted on February 1, 2022, identified 6032 studies published between May 1, 2018, and January 31, 2022 (PubMed = 5455, CENTRAL = 536, ICTRP = 41). Of this, 102 duplicate studies were excluded. After the titles and abstracts of 5930 studies were screened, two were identified. A study (NCT04754802) using PH98 Nasal Spray was excluded because no results were reported. Finally, only one study,[15] JNJ-42165279, was included in this systematic review. Consequently, the results of the meta-analysis for SSRIs and SNRI remained unchanged after the updated search.

3.2 | Characteristics of included studies

RCT studies using SSRI or SNRI included in this review were shown in Table 1. The largest number of studies using SSRI was Paroxetine with 19 studies, and followed by Fluvoxamine with five studies, Sertraline with five studies, Escitalopram with three studies, and Citalopram with one study. While SNRI studies included Venlafaxine with five studies and Desvenlafaxine with one study. SSRI studies were evaluated with low quality of evidence and SNRI studies were evaluated with very low quality of evidence because those were reported that inadequate information about randomization and allocation concealment. The risk of bias was shown in Figure S1.

3.3 | SSRIs

3.3.1 | Response rate

The forest plot of response rate of effect sizes and 95% CI in 26 studies using SSRIs are shown in Figure 2. The pooled estimates of all SSRIs studies showed that statistically significant differences in response rate between SSRI and placebo (RR = 1.62; 95%CI, 1.46, 1.79). Significant heterogeneity was also found in 26 SSRIs studies ($P = .005$; $I^2 = 47\%$). The asymmetric funnel plot revealed that the possibility of publication bias, with several smaller studies clustering to the right of the mean (Figure 3).

3.3.2 | LSAS score reduction

The forest plot of LSAS score reduction of effect sizes and 95% CI in 16 studies using SSRIs are shown in Figure S2. The pooled estimates of SSRIs studies showed that statistically significant differences in LSAS score reduction between SSRI and placebo (mean difference = −9.65; 95%CI, −12.78, −6.52). Significant heterogeneity was also found in 16 SSRIs studies ($P = .003$; $I^2 = 64\%$). The asymmetric funnel plot revealed that the possibility of publication bias, with several smaller studies clustering to the left of the mean (Figure S3).

3.3.3 | Dropout rate

The forest plot of dropout rate of effect sizes and 95% CI in 28 studies using SSRIs are shown in Figure S4. The pooled estimates of all SSRIs studies showed that no statistically significant differences in all reasons of dropout rate between SSRI and placebo (RR = 1.03; 95%CI, 0.91, 1.15). Significant heterogeneity was not found in all SSRIs studies ($P = .16$; $I^2 = 21\%$). The asymmetric funnel plot revealed that the possibility of publication bias, with several smaller studies clustering to the left of the mean (Figure S5).

3.4 | SNRI (VENLAFAXINE)

3.4.1 | Response rate

The forest plot of response rate of effect sizes and 95% CI in five studies using SNRIs are shown in Figure 4. The pooled estimates of all SNRIs studies showed that statistically significant differences in response rate between SNRI and placebo (RR = 1.57; 95%CI, 1.38, 1.80). No significant heterogeneity was found in five SNRIs studies ($P = .90$; $I^2 = 0\%$). The publication bias shown in the funnel plot is unclear due to small sample size (Figure S6).

3.4.2 | LSAS score reduction

The forest plot of LSAS score reduction of effect sizes and 95% CI in four studies using SNRIs are shown in Figure S7. The pooled estimates of SNRIs studies show that statistically significant differences in LSAS score reduction between SNRI and placebo (mean difference = −11.72; 95%CI, −15.70, −7.75). No significant heterogeneity was found in four SNRIs studies ($P = .68$; $I^2 = 0\%$). The publication bias shown in the funnel plot is unclear due to small sample size (Figure S8).

3.4.3 | Dropout rate

The forest plot of dropout rate of effect sizes and 95% CI in five studies using SNRIs are shown in Figure S9. The pooled estimates of

TABLE 1 Characteristics of included studies

No	Author	Year	Intervention (n)	Dose (mg)	Duration of intervention (wk)	Mean age[a] (y)	Sex[a] male/female	Diagnostic measure	Outcomes used in this review
1	Allgulander[32]	1999	Paroxetine (44) Placebo (48)	20–50	12	41	48/44	DSM-IV	CGI, LSAS, Dropout
2	Allgulander[27]	2004	Paroxetine (144) Venlafaxine (144) Placebo (146)	20–50	12	38.8	183/206	DSM-IV	Dropout
3	Asakura[20]	2007	Fluvoxamine 300 mg (89) Fluvoxamine 150 mg (93) Placebo (89)	300 150	10	38.6	179/86	DSM-IV	CGI, LSAS
4	Asakura[11]	2008	Paroxetine 40 mg (133) Paroxetine 20 mg (132) Placebo (130)	40 20	12	37.0	186/209	DSM-IV	CGI, LSAS, Dropout
5	Askura[12]	2016	Escitalopram 20 mg (193) Escitalopram 10 mg (198) Placebo (196)	20 10	12	33.0	260/327	DSM-IV	CGI, LSAS, Dropout
6	Baldwin[16]	1999	Paroxetine (139) Placebo (151)	20–50	12	36	133/157	DSM-IV	CGI, LSAS, Dropout
7	Blomhoff[23]	2001	Sertraline (98) Placebo (98) Exposure (93) Sertraline and exposure (98)	50–150	24	40.4	153/234	DSM-IV	CGI, Dropout
8	Book[33]	2008	Paroxetine (21) Placebo (21)	10–60	16	29	22/20	DSM-IV	CGI, LSAS,
9	Davidson[21]	2004a	Fluvoxamine (139) Placebo (140)	100–300	12	37.3	179/100	DSM-IV	CGI, LSAS, Dropout
10	Davidson[34]	2004b	Fluoxetine (57) Placebo (60)	10–40	14	36.6	66/51	DSM-IV	CGI, Dropout
11	Furmark[35]	2005	Citalopram (12) GR205171 (12) Placebo (12)	20–40	6	31.6	17/19	DSM-IV	CGI, LSAS
12	Kasper[25]	2005	Escitalopram (181) Placebo (177)	10–20	12	38	195/163	DSM-IV	CGI, Dropout
13	Katzelnick[36]	1995	Sertraline (6) Placebo (6)	50–200	10	42.6	8/4	DSM-IIIR	LSAS, Dropout
14	Kobak[37]	2002	Fluoxetine (30) Placebo (30)	20–60	14	39.5	25/35	DSM-IV	CGI, LSAS, Dropout

TABLE 1 (Continued)

No	Author	Year	Intervention (n)	Dose (mg)	Duration of intervention (wk)	Mean age[a] (y)	Sex[a] male/female	Diagnostic measure	Outcomes used in this review
15	Lader[26]	2004	Escitalopram 20 mg (170) Escitalopram 10 mg (167) Escitalopram 5 mg (167) Paroxetine 20 mg (169) Placebo (166)	20 10 5 20	12–24	37.0	394/445	DSM-IV	CGI, Dropout
16	Lepola[17]	2004	Paroxetine (186) Placebo (184)	12.5–37.5	12	38.9	270/100	DSM-IV	CGI, Dropout
17	Liebowitz[18]	2002	Paroxetine (389) Placebo (95)	20–60	12	37.0	225/159	DSM-IV	CGI, LSAS, Dropout
18	Liebowitz[38]	2003	Sertraline (211) Placebo (204)	25–200	12	35.1	247/168	DSM-IV	CGI, LSAS, Dropout
19	Liebowitz[28]	2005a	Venlafaxine (133) Placebo (144)	75–225	12	35.4	148 /123	DSM-IV	CGI, LSAS, Dropout
19	Liebowitz[28]	2005b	Paroxetine (136) Venlafaxine (133) Placebo (144)	20–50 75–225	12	36.3	221/192	DSM-IV	CGI
20	NCT00273039		Paroxetine (36) Placebo (71)	20–30	12	34.4	60/44	DSM-IV	Dropout
21	NCT00318669		Paroxetine (267) Placebo (133)	20, 40	12	37.0	186/209	DSM-IV Text Revision	CGI, Dropout
22	NCT00397722		Paroxetine (42) GW876008 (164) Placebo (88)	20–30	12	37.4	155/139	DSM-IV	CGI, Dropout
23	NCT00403962		Paroxetine (68) Placebo (65)	7.5	12	40.3	54/74	DSM-IV	CGI, Dropout
24	NCT00470483		Paroxetine (17) Placebo (16)	5–20	8	22.9	5/28	DSM-IV	Dropout
25	NCT01316302		Desvenlafaxine (30) Placebo (33)	50–100	12	40.0	29/34	DSM- IV Text Revision	CGI, LSAS, Dropout
26	Nordahl[39]	2016	Paroxetine (26) Placebo (26)	20–60	12	30.9	26/26	DSM-IV	CGI, LSAS, Dropout
27	Randall[40]	2001	Paroxetine (6) Placebo (9)	20–60	8	35.5	13/2	DSM-IV	CGI, Dropout
28	Rickels[30]	2004	Venlafaxine (126) Placebo (135)	75–225	12	41.5	150 /111	DSM-IV	CGI, LSAS
29	Stein[41]	1996	Paroxetine (8) Placebo (8)	10–50	12	not specified	24/6	DSM-IV	Dropout

(Continues)

TABLE 1 (Continued)

No	Author	Year	Intervention (n)	Dose (mg)	Duration of intervention (wk)	Mean age[a] (y)	Sex[a] male/female	Diagnostic measure	Outcomes used in this review
30	Stein[19]	1998	Paroxetine (94) Placebo (93)	20–50	12	36.3	81/106	DSM-IV	CGI, LSAS, Dropout
31	Stein[22]	1999	Fluvoxamine (48) Placebo (44)	50–300	12	39.4	59/32	DSM-IV	CGI, LSAS, Dropout
32	Stein[31]	2005	Venlafaxine (238) Placebo (126)	75–225	28	36.9	212 /152	DSM-IV	CGI, LSAS, Dropout
33	Tauscher[42]	2010	Paroxetine (38) LY686017 (77) Placebo (74)	20	12	not specified	not specified	DSM- IV Text Revision	LSAS
34	Van Ameringen[24]	2001	Sertraline (135) Placebo (69)	50–200	20	35.7	114/90	DSM-IV	CGI, Dropout
35	Van Vliet[43]	1994	Fluvoxamine (15) Placebo (15)	50–150	12	35.2	13/17	DSM-IIIR	Dropout
36	Westernberg[44]	2004	Fluvoxamine (149) Placebo (151)	50–300	12	33.0	143 /157	DSM-IV	CGI, Dropout

Abbreviations: CGI, Clinical Global Impression; DSM, Diagnostic and Statistical Manual; LSAS, Liebowitz Social Anxiety Scale.
[a]Intent-to-treat population.

all SNRIs studies showed that no statistically significant differences in all reasons of dropout rate between SNRI and placebo (RR = 0.89; 95%CI, 0.78, 1.02). No significant heterogeneity was found in five SNRIs studies ($P = .43$; $I^2 = 0\%$). The publication bias shown in the funnel plot is unclear due to small sample size (Figure S10).

3.5 | Response rates of SSRIs and LSAS reduction in Japanese studies

To examine the response rate and efficacy of the medication in Japanese SAD patients, we analyzed studies of SSRIs in Japan separately from those in other countries. The forest plot of response rate of effect sizes and 95% CI in three studies using SSRIs for Japanese patients with SAD are shown in Figure 5. The pooled estimates showed that statistically significant differences in response rate between SSRI and placebo (RR = 1.44; 95%CI, 1.46, 1.79). No significant heterogeneity was found in three SSRIs studies ($P = .00$; $I^2 = 0\%$). Meanwhile, the pooled estimates of studies conducted in countries other than Japan were also significantly different in response rate between SSRI and placebo (RR = 1.67; 95%CI, 2.12, 2.72; Figure 6); however, significant heterogeneity was found in 23 SSRIs studies ($P = .002$; $I^2 = 52\%$). Additionally, regarding LSAS score reduction, the forest plot of response rate of effect sizes and 95% CI in three studies using SSRIs for Japanese patients with SAD are shown in Figure S11. The pooled estimates showed that statistically significant differences in LSAS score reduction between SSRI and placebo (standardized mean difference = −0.34; 95%CI, −0.48, −0.21). No significant heterogeneity was found in three SSRIs studies ($P = .46$; $I^2 = 0\%$). Meanwhile, the pooled estimates of studies conducted in countries other than Japan were also significantly different in LSAS score reduction between SSRI and placebo (standardized mean difference = −0.44; 95%CI, −0.59, −0.29; Figure S12). However, significant heterogeneity was found in 13 SSRIs studies ($P = .02$; $I^2 = 49\%$).

3.6 | Sensitivity analyses

We conducted sensitivity analyses to examine the impact of each study using SSRIs on heterogeneity: When Allgurander 1999 was excluded, the I-square decreased from 47% to 31% (Response rate = 1.62–1.58); however, when Furmark 2005 was additionally excluded, it decreased from 31% to 30%. For the studies using SSRIs other than Japan, the I^2 decreased from 52% to 37% (Response rate = 1.67–1.62) when Allgurander 1999 was excluded; however, there was no further decrease when Furmark 2005 was additionally excluded. These results indicated that Allgurander 1999 could increase the heterogeneity.

4 | DISCUSSION

We conducted a systematic review of pharmacotherapy for SAD, including a Japanese database. In addition, the study by Williams et al[8]

Study or Subgroup	SSRIs Events	SSRIs Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Allgulander 1999	31	44	4	48	1.0%	8.45 [3.25, 22.03]
Asakura 2007	82	182	27	89	4.4%	1.49 [1.04, 2.11]
Asakura 2008	66	133	47	130	5.4%	1.37 [1.03, 1.83]
Asakura 2016	106	193	74	196	6.6%	1.45 [1.17, 1.81]
Baldwin 1999	90	137	47	145	5.8%	2.03 [1.56, 2.64]
Blomhoff 2001	35	87	21	88	3.2%	1.69 [1.07, 2.65]
Book 2008	11	20	6	22	1.4%	2.02 [0.92, 4.44]
Davidson 2004a	41	121	21	126	3.1%	2.03 [1.28, 3.23]
Davidson 2004b	20	39	11	36	2.3%	1.68 [0.94, 3.00]
Furmark 2005	6	12	1	12	0.3%	6.00 [0.85, 42.59]
Kasper 2005	96	177	69	176	6.5%	1.38 [1.10, 1.74]
Kobak 2002	12	30	9	30	1.7%	1.33 [0.66, 2.69]
Lader 2004	337	490	82	164	7.8%	1.38 [1.17, 1.62]
Lepola 2004	106	186	56	184	6.0%	1.87 [1.46, 2.41]
Liebowitz 2002	40	89	26	92	3.8%	1.59 [1.07, 2.37]
Liebowitz 2003	96	205	51	196	5.6%	1.80 [1.36, 2.38]
Liebowitz 2005b	85	133	52	144	6.0%	1.77 [1.38, 2.28]
NCT00318669	135	265	47	127	6.0%	1.38 [1.07, 1.78]
NCT00397722	24	42	32	88	4.0%	1.57 [1.07, 2.30]
NCT00403962	17	65	18	62	2.4%	0.90 [0.51, 1.58]
Nordahl 2016	9	21	3	23	0.7%	3.29 [1.02, 10.53]
Randall 2001	4	6	2	9	0.5%	3.00 [0.78, 11.54]
Stein 1998	50	91	22	92	3.7%	2.30 [1.53, 3.46]
Stein 1999	18	42	10	44	1.9%	1.89 [0.99, 3.60]
Van Ameringen 2001a	71	134	20	69	3.8%	1.83 [1.22, 2.73]
Westerberg 2004	73	149	66	151	6.2%	1.12 [0.88, 1.43]
Total (95% CI)		**3093**		**2543**	**100.0%**	**1.62 [1.46, 1.79]**
Total events	1661		824			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 47.18$, df = 25 (P = 0.005); $I^2 = 47\%$
Test for overall effect: Z = 9.48 (P < 0.00001)

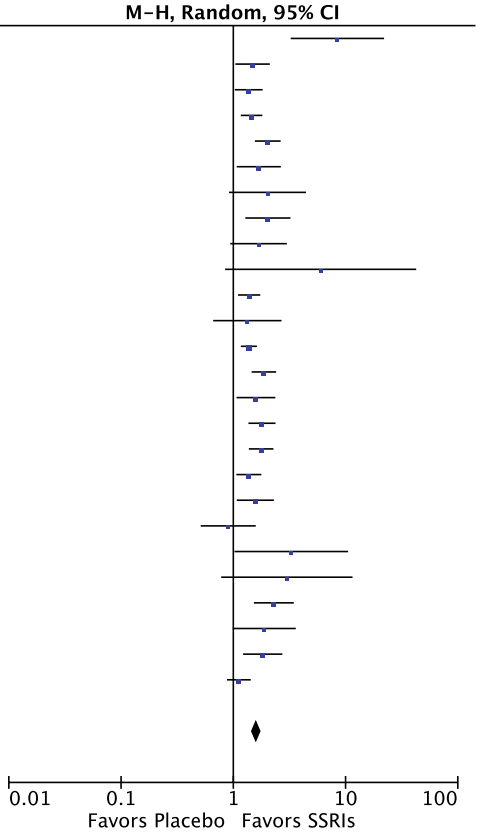

FIGURE 2 The forest plot of response rate of 26 studies using SSRIs

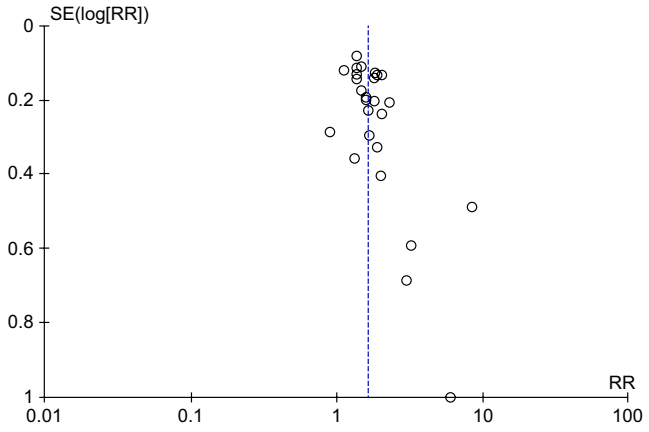

FIGURE 3 The funnel plot of response rate of 26 studies using SSRIs

was re-examined as an existing systematic review with an additional period. The current study has yielded two new findings. First, the response rate and LSAS reduction of SAD with venlafaxine were equivalent to those of SSRIs. The results showed that SSRIs and venlafaxine had significant response rates and reductions in severity, while the dropout rate was not statistically significantly different from placebo. Second, the response rate of Japanese patients with SAD to SSRIs was lower than that of other countries. Focusing on Japanese patients with SAD, there was a significant response rate to SSRIs and a significant improvement in SAD symptom severity. However, compared to studies conducted in other countries, the response rate and the improvement in SAD symptom severity were relatively low.

Regarding SSRIs, 32 studies were included, with 18 RCTs of paroxetine which were the largest number of studies included. As for Japanese studies, two RCTs on paroxetine[11] and escitalopram[12] in the present systematic review. The RCT for paroxetine was a Japanese article, which was imported from a Japanese database. In this study, 399 Japanese were randomly assigned to three groups: paroxetine 20 mg/d group, paroxetine 40 mg/d group, or placebo group. The two groups of active drug had significantly higher response rates (53.5% for paroxetine 20 mg/d group and 51.2% for paroxetine 40 mg/d group) than placebo and significantly lower LSAS reductions ($P = .007$ for paroxetine 20 mg group, $P = .025$ for paroxetine 40 mg group) after 12 weeks than placebo.[11] Internationally, paroxetine is the medication with the greatest number of RCTs, and several studies[16–19] have reported significant response rates and improvements in social anxiety symptoms over placebo. Other than paroxetine, fluvoxamine[20–22] and sertraline[23,24] have been reported to have significant response rates and improvement rates in social anxiety symptoms with several RCTs. Only three studies were identified on escitalopram; however, all of the studies reported significant response rates. The current review identified an RCT,[12] which was analyzed in addition to the two studies[25,26] included in the previous systematic review.[8] After all, there was little

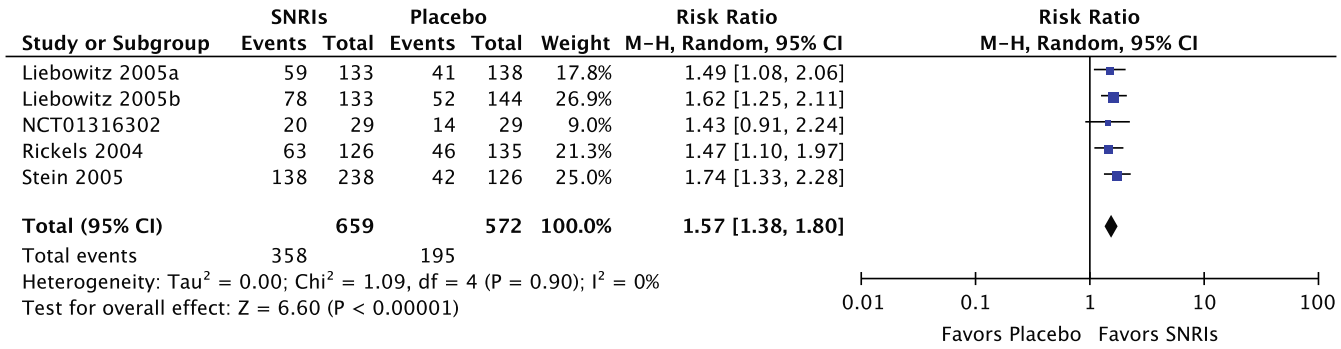

FIGURE 4 The forest plot of response rate of five studies using SNRIs

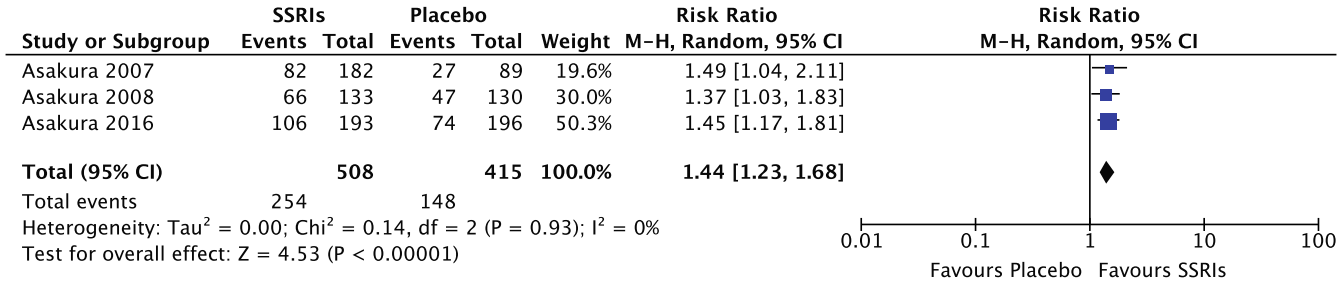

FIGURE 5 The forest plot of response rate of three studies in Japan using SSRIs

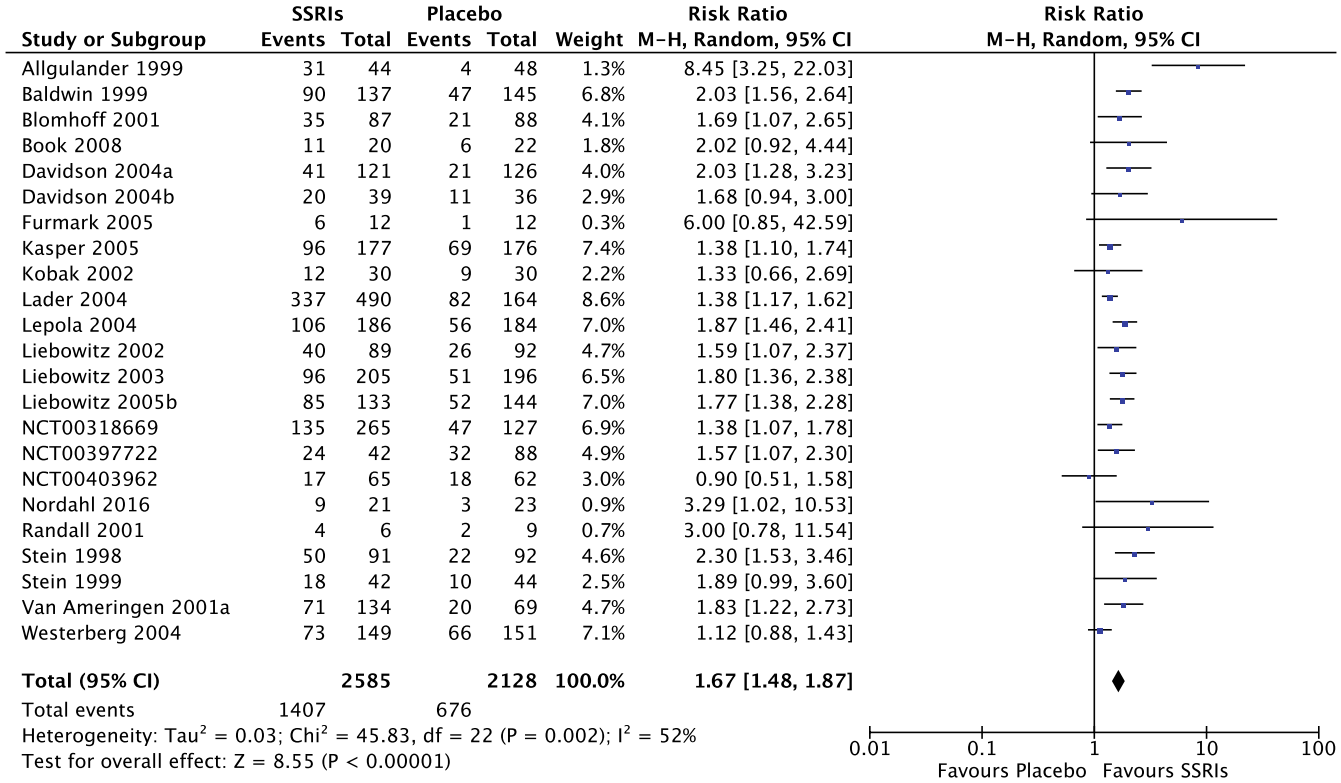

FIGURE 6 The forest plot of response rate of 23 studies in countries other than Japan using SSRIs

variation in the response rate of SSRIs among the medications, and the dropout rates were not significantly different from placebo for either medication. Paroxetine in particular had the highest response rate, but the SSRIs available in Japan (eg, fluvoxamine and escitalopram) also had comparable significant response rates, LSAS score reduction, and not significant dropout rates. The quality of studies using SSRIs is low to very low quality, and caution should be taken in interpreting the results. In addition, the funnel plot showed a clear imbalance, so it is

likely that a small number of studies were not reported, which may indicate a publication bias.

On the contrary, the analysis of SNRIs was based only on studies of venlafaxine or desvenlafaxine, and no data were available from RCTs of other SNRIs. In this systematic review, one new RCT on desvenlafaxine (NCT1316302) was added to the five RCTs on venlafaxine[27–31] included in the previous systematic review. During the process of this systematic review, an error was found in the data on venlafaxine in a previous systematic review. Specifically, the response rate data for the RCT reported by Rickels et al[30] were given as venlafaxine 43/126 and placebo 68/135 in the previous systematic review,[8] but the original data showed that the response rate after 12 weeks was 50% (63/126) for venlafaxine and 34% (46/135) for placebo.[30] The latter data were used in the analysis and recalculated in the present study, resulting in a significant response rate for venlafaxine (RR 1.57; 95% CI, 1.38–1.80). Based on the above modifications, we concluded that venlafaxine could be an effective option for pharmacotherapy on SAD. As for medications other than SSRIs and SNRIs, there was one RCT each of vortioxetine[13] and vilazodone,[14] but these medications were not reported in previous studies and could not be analyzed for meta-analysis. Pharmacotherapies for SAD other than SSRIs and SNRIs are needed to further study.

RCTs in Japanese subjects were low heterogeneity and involved relatively homogeneous populations, but the number of RCTs was too small to fully examine pharmacological response in Japanese SAD patients. Meanwhile, RCTs conducted in countries other than Japan were more heterogeneous, even if the sensitivity analysis was considered, but response rates and improvement in SAD symptoms were higher than in the Japanese studies. These results suggest that the efficacy of pharmacotherapy for Japanese patients with SAD could be low; however, further data accumulation is needed to draw any conclusions.

There are several limitations in this study. This study based much of its data on a previous systematic review, and there were only a few new results that could be added. Many of the studies included in the analysis of this study provided insufficient information on randomization and allocation concealment. This insufficient information leaded to a decline in the overall quality of research. Concerning the heterogeneity, the meta-analysis of studies on SSRIs and studies on SSRIs other than Japan found moderate heterogeneity. Hence, we conducted a sensitivity analysis and found a negligible heterogeneity by excluding the study31 reported by Allgurander in 1999. The author discussed in the original paper that the inclusion of only previously untreated cases in a single-center study affected the high response rate of subjects on paroxetine. Meanwhile, the response rate of studies on SSRIs and studies on SSRIs other than Japan were scarcely changed. Consequently, the results of the present meta-analysis are considered to be valid.

5 | CONCLUSIONS

In the present study, we conducted a meta-analysis of the response rate, efficacy, and dropout rate of pharmacotherapy for SAD by adding data to an existing systematic review with the inclusion of a database in Japanese. Significant response rates were observed for SSRIs and venlafaxine, which were considered to be effective medications. However, the results should be interpreted cautiously because they do not eliminate the risk of various bias.

AUTHOR CONTRIBUTIONS

Conceptualization: ES, TI, and SA. Study design: NM, YF, and SA. Data acquisition: NM, YF, and HI. Data analysis: NM. Writing—original draft: NM. Visualization: NM. Writing—review and editing: NM, YF, SA, HI, HY, NY, and YK. Supervision: ES and TI. Validation: NM, YF, SA, ES, and TI.

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CONFLICT OF INTEREST

The authors have declared that there are no conflicts of interest in relation to the subject of this study. NM has received grant from Okamoto mental health foundation. SA received honoraria from Tanabe Mitsubishi Pharma, Mochida Pharmaceutical, Yoshitomiyakuhin and Shionogi & Co., LTD. HI reports lecture fees from Mochida Pharmaceutical and Otsuka Pharmaceutical, personal fees from Mitsubishi-Tanabe pharma, personal fees from Kyowa pharmaceutical, outside the submitted work. Takeshi Inoue has received personal fees from Mochida Pharmaceutical, Takeda Pharmaceutical, Eli Lilly, Janssen Pharmaceutical, MSD, Taisho Toyama Pharmaceutical, Yoshitomiyakuhin, and Daiichi Sankyo; grants from Shionogi, Astellas, Tsumura, and Eisai; and grants and personal fees from Otsuka Pharmaceutical, Dainippon Sumitomo Pharma, Mitsubishi Tanabe Pharma, Kyowa Pharmaceutical Industry, Pfizer, Novartis Pharma, and Meiji Seika Pharma; and is a member of the advisory boards of Pfizer, Novartis Pharma, and Mitsubishi Tanabe Pharma. ES reports a joint research fund under contract from Sumitomo Dainippon Pharma, outside the submitted work.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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