

# Optimal treatment of social phobia: systematic review and meta-analysis

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**Abstract:** This article proposes a number of recommendations for the treatment of generalized social phobia, based on a systematic literature review and meta-analysis. An optimal treatment regimen would include a combination of medication and psychotherapy, along with an assertive clinical management program. For medications, selective serotonin reuptake inhibitors and dual serotonin-norepinephrine reuptake inhibitors are first-line choices based on their efficacy and tolerability profiles. The nonselective monoamine oxidase inhibitor, phenelzine, may be more potent than these two drug classes, but because of its food and drug interaction liabilities, its use should be restricted to patients not responding to selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors. There are other medication classes with demonstrated efficacy in social phobia (benzodiazepines, antipsychotics, alpha-2-delta ligands), but due to limited published clinical trial data and the potential for dependence and withdrawal issues with benzodiazepines, it is unclear how best to incorporate these drugs into treatment regimens. There are very few clinical trials on the use of combined medications. Cognitive behavior therapy appears to be more effective than other evidence-based psychological techniques, and its effects appear to be more enduring than those of pharmacotherapy. There is some evidence, albeit limited to certain drug classes, that the combination of medication and cognitive behavior therapy may be more effective than either strategy used alone. Generalized social phobia is a chronic disorder, and many patients will require long-term support and treatment.

**Keywords:** social phobia, social anxiety disorder, psychotherapy, cognitive behavior therapy, antidepressant

## Introduction

Social phobia (also known as social anxiety disorder) is an anxiety disorder in which there is a “marked and persistent fear of social or performance situations in which embarrassment may occur”.<sup>1</sup> It was first included in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) in 1980<sup>2</sup> and is included in the section on anxiety disorders. DSM has the specifier of “generalized” relating to when fears are related to most social situations. By exclusion, the unspecified “nongeneralized” form relates to specific situations, and in the literature is often referred to as “nongeneralized social phobia”. For the remainder of this article, we have chosen to focus on generalized social phobia (hereafter simply referred to as social phobia). Generalized social phobia is the more relevant disorder to general psychiatric clinical work.

Social phobia has an early onset, with the median age of onset in the National Comorbidity Survey of 16 years.<sup>3</sup> The most commonly reported fears relate to public speaking or speaking up in a meeting or a class.<sup>4</sup> The disorder is associated with

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significant disability. Patients with social phobia are more likely to utilize medical outpatient clinics, receive lower incomes, be less likely to earn college degrees, or attain managerial, technical, or professional occupations<sup>3,5,6</sup> than people not suffering with social phobia. They are also more impaired in family relationships, romantic relationships, and desire to live, with 21.9% having attempted suicide.<sup>6,7</sup> The course of social phobia tends to be chronic, with a long duration of illness<sup>8</sup> and low rates of recovery.<sup>9</sup>

Social phobia has a high degree of comorbidity with other psychiatric disorders. Eighty-one percent of people suffering from social phobia reported at least one other lifetime DSM-III-R disorder in the National Comorbidity Survey.<sup>3</sup> The odds ratio (OR) of having a second anxiety disorder is increased (range 7.1–8.7).<sup>3</sup> Between 16.6%<sup>10</sup> and 35.8%<sup>6</sup> of sufferers experience major depressive disorder, with social phobia preceding the onset of major depressive disorder by 12 years.<sup>6</sup> Rates of concurrent alcohol dependence are 27.3%, and concurrent alcohol abuse occurs in 11.3%<sup>6</sup> to 20.9%<sup>10</sup> of patients with social phobia. For patients with social phobia and a comorbid alcohol misuse disorder, almost 80% developed social phobia before the alcohol misuse disorder.<sup>11</sup> This seems to be the pattern with other comorbid conditions, with social phobia being the primary disorder in 71.4%.<sup>3,6</sup> Patients who have social phobia and a comorbid alcohol disorder have an increased rate of comorbid psychiatric disorders, with 97% having at least one additional Axis I disorder, and 71.7% having a personality disorder.<sup>11</sup>

Recent data from the cross-sectional World Mental Health surveys<sup>12</sup> provide cross-national comparisons of social phobia diagnosed by DSM-IV Composite International Diagnostic Interview in the general populations of developed and developing countries. These data show great variation in 12-month prevalence. Rates are lowest in China and Japan (0.3% and 0.5%, respectively), range from 0.6% to 1.4% in European countries, and are somewhat higher in the Ukraine (1.5%), South Africa (1.9%), Mexico (1.9%), and Colombia (2.8%). Rates then jump to 5.1% in New Zealand and 6.8% in the US. Explanations for these differences are likely to include both substantive and methodological reasons. The World Mental Health survey data indicate that social phobia has one of the earliest ages of onset amongst the mental disorders and yet is also one of the most undertreated anxiety disorders. Data from the New Zealand survey, the largest of the World Mental Health collaborating surveys, show that fewer than 5% of those meeting the criteria for social phobia sought treatment in the year of onset, and only 36% of those with a lifetime diagnosis of social phobia sought treatment from a health

professional at some stage.<sup>12</sup> This latter statistic compares with 57% for generalized anxiety disorder, 63% for panic disorder, 54% for agoraphobia, and 50% for post-traumatic stress disorder.

There are a number of treatment options for social phobia, including medication, psychotherapy, and their combination. Although there have been a number of reviews of medications,<sup>13,14</sup> psychological treatment,<sup>15,16</sup> and combined treatments<sup>17,18</sup> for social phobia, and the development of clinical guidelines,<sup>18</sup> there has been no synthesis of these data to identify characteristics for optimal overall management of social phobia. Patients with social phobia are difficult to engage with psychiatric services, and to date there are no published data to identify how to improve treatment engagement or adherence. The objective of this systematic review and meta-analysis was to identify optimal treatments for social phobia, based on a systematic review of published clinical trial data.

## Methods

### Meta-analysis of treatment trials

We performed a systematic review and meta-analysis of clinical trials using drugs, psychotherapy, or their combination, in social phobia. For the drug trials, the search methods were intended to identify all randomized, double-blind, parallel-group treatment trials in social phobia. For the psychological treatment trials, the search aimed to identify all randomized controlled trials (RCT). The search included published and unpublished studies, electronic database searches, searches of clinical and pharmaceutical trial registers, and personal communication with study authors. Studies were identified and obtained between September 2011 and January 2012 using electronic databases (Embase [1974 to the present] and Medline [1950 to the present]); reference lists of identified articles and other electronic search tools; clinical trials websites (<http://www.clinical-trialresults.org>, <http://clinicaltrials.gov>, <http://apps.who.int/trialsearch/>); and, when required, communication with study authors. The following Boolean phrases were used when searching electronic databases and other electronic search engines: “randomized controlled trial”, “treatment”, “drug”, “psychotherapy”, “psychological treatment”, “cognitive behavior therapy”, “cognitive therapy”, “exposure therapy”, “social phobia”, and “social anxiety disorder”.

### Inclusion criteria

We sought to identify RCT, either placebo-controlled or active-controlled. Only publications in English were considered.

Studies that did not include information on treatment outcome were excluded. Study participants were adults who were diagnosed with DSM-III, DSM-III-R, or DSM-IV criteria for social phobia/social anxiety disorder. Data from maintenance or discontinuation phases were not collected. We did not include trials of exploratory agents, eg, neurokinin-1 antagonists or d-cycloserine, in this review. The relevance of identified papers was initially screened using title and abstract. Full manuscripts of studies of interest were screened according to inclusion criteria. Social phobia treatment studies involving medications generally include a range of clinician-rated and patient-rated outcome measures. For this analysis, we chose one endpoint, ie, the proportion of responders based on clinician assessments. In most studies, a responder was defined as someone who achieved a score of 1 or 2 on the seven-point Clinical Global Impression of Change (CGI) scale.<sup>19</sup> This represents a rating of score of very much or much improved (score of 1 or 2, respectively). In four studies, response was defined as a 50% reduction in a clinician-rated instrument (eg, Liebowitz Social Anxiety Scale<sup>107</sup> or Hamilton Anxiety Scale<sup>108</sup>) or, in one case, a self-rated instrument (Fear Questionnaire)<sup>109</sup>. Previous meta-analyses have shown that changes in the CGI are broadly similar to changes in other clinician-rated and patient-rated instruments.<sup>20,21</sup> The majority of comparative psychotherapy trials do not report responder rates, so a narrative review is provided.

## Data synthesis and analysis

All analyses were performed using Review Manager (RevMan) 5.0 (Cochrane Collaboration, 2008; <http://www.cc-ims.net/RevMan>). For rates of treatment response, Mantel-Haenszel OR were calculated using a random effects model. The  $I^2$  statistic was used to assess heterogeneity.

## Results

### Study identification and selection

The search strategy identified 410 papers. Based on a review of study title and abstract, 183 were selected for detailed review. Reasons for noninclusion included ineligible study design (eg, nonblinded dosing, continuation treatment trial, crossover trial), response data not provided in results, duplicate data presentation, and review articles. Ultimately, 41 papers were selected for inclusion in the meta-analysis.

### Antidepressant drugs

#### Selective serotonin reuptake inhibitors

This class of drugs is the most extensively tested in patients with social phobia, with 17 placebo-controlled

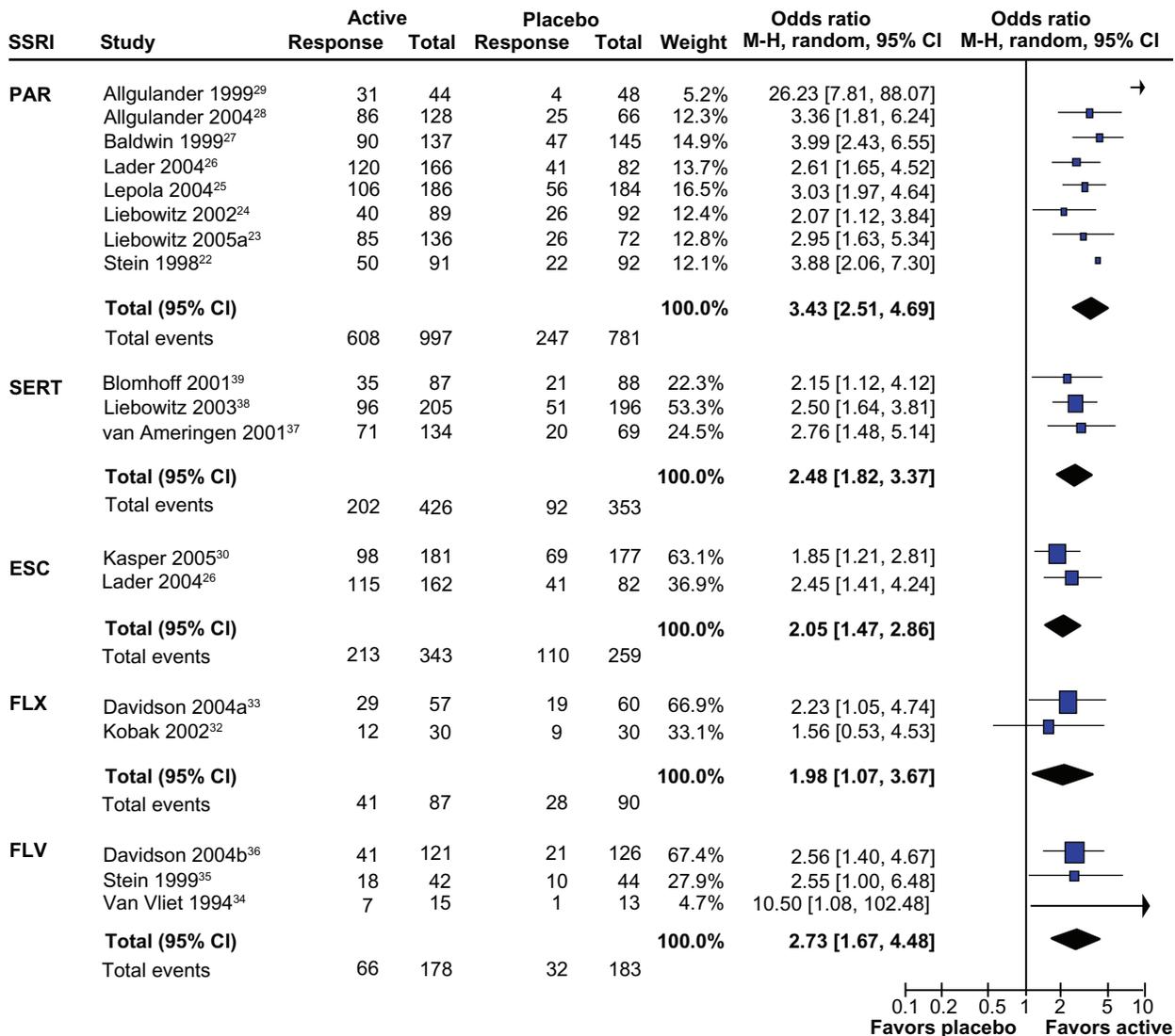
acute treatment RCT reported. Almost half of the studies studied paroxetine,<sup>22–29</sup> with 2–3 studies each for escitalopram,<sup>26,30</sup> fluoxetine,<sup>31–33</sup> fluvoxamine,<sup>34–36</sup> and sertraline.<sup>37–39</sup> The pooled OR for response to each selective serotonin reuptake inhibitor (SSRI) ranges between 1.98 for fluoxetine and 3.41 for paroxetine (Figure 1). With one exception, SSRIs had significantly greater CGI response rates compared with placebo. The single negative study (fluoxetine)<sup>32</sup> was of adequate duration and used a high fluoxetine dose (60 mg/day), but was relatively small in size ( $n = 30$  per arm), and may thus have been underpowered to show a difference from placebo. There was significant heterogeneity associated with one study,<sup>29</sup> but its exclusion in a sensitivity analysis had little effect on the pooled OR for paroxetine studies (3.43 decreased to 3.09). In general, SSRIs showed separation from placebo by weeks 4–6 on a number of response or other outcome measures, however SSRI-placebo differences tended to increase out to 12 weeks of treatment. There have been four studies assessing the effect of continuation treatment with SSRIs in patients who have responded to acute treatment.<sup>40–43</sup> In these relapse prevention studies, patients were randomized to remain on their SSRI or were switched to placebo, under double-blind conditions. All four studies showed robust effects of the SSRIs in preventing relapse of social phobia (pooled OR 0.25, 95% confidence interval [CI] 0.18–0.35).<sup>44</sup>

#### Serotonin and norepinephrine reuptake inhibitors

Venlafaxine is the only serotonin-norepinephrine reuptake inhibitor (SNRI) studied in RCT in patients with social phobia, but improvements in social phobia symptom ratings have also been shown in an open-label trial of the SNRI, duloxetine.<sup>45</sup> All five reported studies<sup>23,28,46–48</sup> have shown significantly greater response rates for venlafaxine compared with placebo (Figure 2, OR range for treatment response 1.89–3.78). Four of five studies used flexible dosing, with mean daily doses of approximately 200 mg/day. The single fixed-dose comparison study<sup>46</sup> showed no differences in outcome measures between 75 mg/day and 150–225 mg/day dose arms, and both separated from placebo. The onset of response across all trials was evident at 4–6 weeks, although maximum separation from placebo continued out to 12 weeks.

#### Monoamine oxidase inhibitors

The first placebo-controlled RCT in social phobia assessed phenelzine, an irreversible monoamine oxidase inhibitor.



**Figure 1** Odds ratios and 95% CI for treatment response in randomized placebo-controlled trials for SSRI.

Response based on CGI for all studies except for Liebowitz Social Anxiety Scale<sup>107</sup> in van Vliet et al.<sup>34</sup> Only the highest ESC dose included for Lader et al.<sup>26</sup>

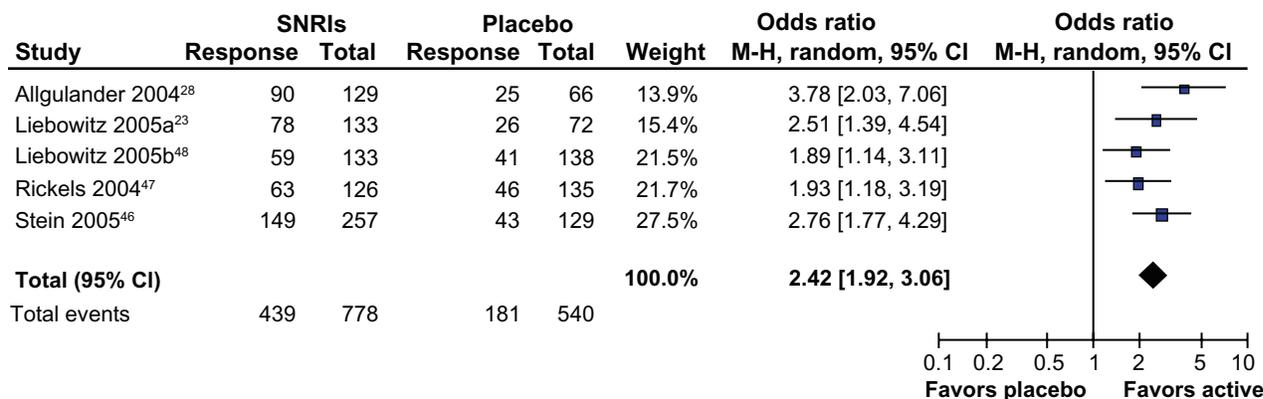
**Abbreviations:** CI, confidence interval; PAR, paroxetine; SERT, sertraline; ESC, escitalopram; FLX, fluoxetine; FLV, fluvoxamine; CGI, Clinical Global Impression; SSRI, selective serotonin reuptake inhibitor; M-H, Mantel-Haenszel odds ratio.

The rationale for using monoamine oxidase inhibitors was because social phobia and atypical depression share the symptom of increased interpersonal sensitivity, and atypical depression is preferentially responsive to monoamine oxidase inhibitors.<sup>49</sup> All four studies with this drug<sup>50–53</sup> showed a significantly greater treatment response compared with placebo; however the pooled OR is heavily influenced by the results from one study<sup>50</sup> (Figure 3, upper panel). Exclusion of this study<sup>50</sup> in a sensitivity analysis reduced the pooled OR from 7.22 to 4.58. There have also been positive open-label studies with tranlycypromine.<sup>54</sup> Reversible selective inhibitors of monoamine oxidase A were developed with the intention of reducing safety concerns due to drug and food interactions with the original nonselective irreversible monoamine oxidase inhibitors.<sup>55</sup> RCT have been

reported for brofaromine,<sup>56–58</sup> a drug that was never submitted for regulatory approval, and moclobemide,<sup>50,59–63</sup> which has been approved in many countries. Excluding brofaromine trials, the pooled OR for response to moclobemide is relatively modest compared with other antidepressant drugs (1.95; 95% CI 1.37–2.79). High heterogeneity ( $I^2 = 69\%$ ) was noted in the analysis of this drug class. Exclusion of three studies of reversible selective inhibitors of monoamine oxidase A (two brofaromine,<sup>56,58</sup> one moclobemide<sup>50</sup>) reduced the heterogeneity to 0%, but also reduced the pooled OR from 2.96 to 1.88.

### Other antidepressants

There are open-label trials in social phobia with the tricyclic antidepressants, imipramine<sup>64</sup> and clomipramine,<sup>65</sup> but no RCT.



**Figure 2** Odds ratios and 95% CI for treatment response in randomized placebo-controlled trials for the serotonin-norepinephrine reuptake inhibitor, venlafaxine. Response based on CGI for all studies.

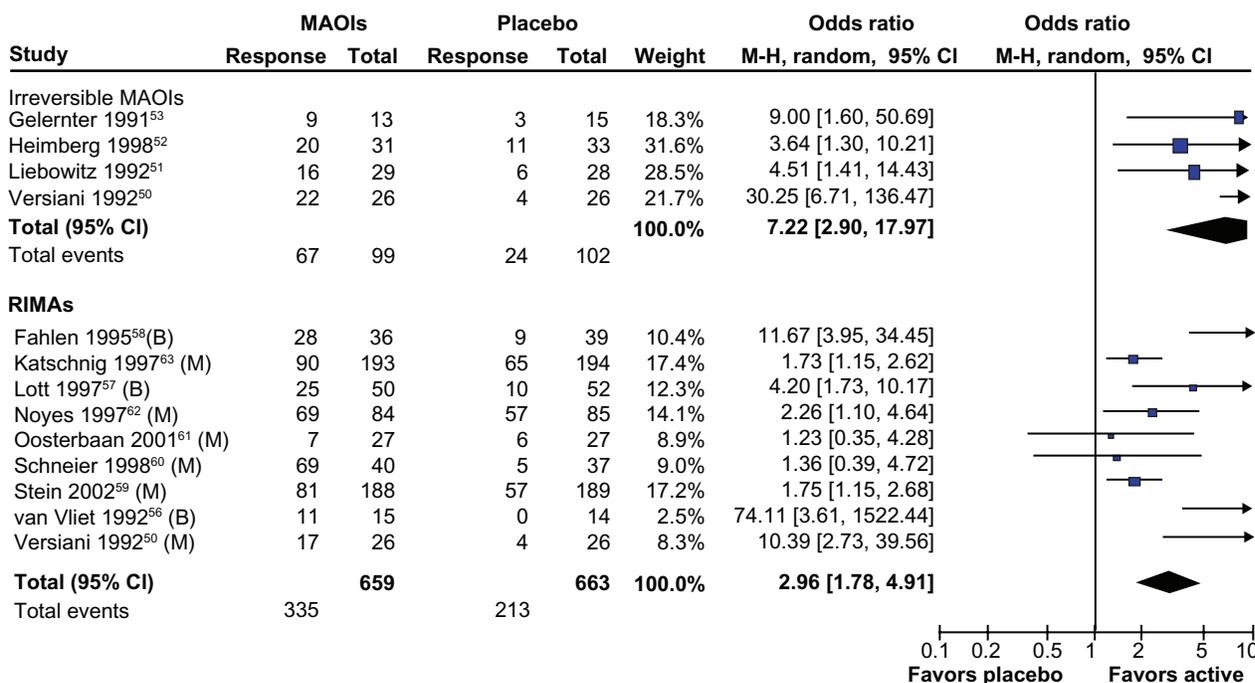
**Abbreviations:** CI, confidence interval; CGI, Clinical Global Impression; M-H, Mantel-Haenszel odds ratio; SNRIs, selective norepinephrine reuptake inhibitors.

Response to atomoxetine, a selective norepinephrine reuptake inhibitor, was not different from placebo.<sup>66</sup> Two placebo-controlled RCT in social phobia have been reported for mirtazapine, an antagonist at 5HT<sub>2</sub>, 5HT<sub>3</sub>, and alpha<sub>2</sub> adrenoceptors. One study showed a greater reduction in relevant outcome scales compared with placebo,<sup>67</sup> whereas the other showed no difference.<sup>68</sup> Both studies were relatively small (n = 30–33 per treatment arm), and both studies are likely to have been underpowered statistically. Nefazodone, an antagonist at 5HT<sub>1a</sub> and 5TH<sub>2a</sub> receptors, did not separate from placebo in a single large clinical trial.<sup>69</sup> The generally negative findings in social

phobia with receptor antagonist antidepressants contrast with the robust positive findings for SSRIs and SNRIs.

### Antiepileptic drugs

The use of antiepileptic drugs in social phobia has been extensively reviewed recently.<sup>70</sup> Only three antiepileptic drugs have been tested in RCT, and show distinct differences in efficacy. Gabapentin and pregabalin are both ligands at the alpha-2 delta site on voltage-gated calcium channels. Functionally, both drugs reduce the release of a range of excitatory neurotransmitters through binding to this site.<sup>71</sup>



**Figure 3** Odds ratios and 95% CI for treatment response in randomized placebo-controlled trials for irreversible and reversible MAOIs.

Response based on CGI for all studies except social phobia subscale of the Fear Questionnaire<sup>108</sup> for Gelernter et al.<sup>53</sup> and the Hamilton Anxiety Scale<sup>109</sup> for van Vliet et al.<sup>56</sup>

**Abbreviations:** B, brofaromine; M, moclobemide; MAOIs, monoamine oxidase inhibitors; CI, confidence interval; M-H, Mantel-Haenszel odds ratio.

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There are three positive RCT with alpha-2 delta ligands<sup>72–74</sup> (see Figure 4). The onset of anxiolytic effects is relatively rapid, occurring within the first week of treatment. The anxiolytic dose-response has only been formally assessed for pregabalin, and efficacy is only evident at the maximum dose (600 mg/day), but not at lower doses.<sup>73,74</sup> This is in contrast with the effect of pregabalin in, eg, generalized anxiety disorder, where the anxiolytic dose-response is seen at much lower doses (150 mg/day).<sup>75</sup> There are no long-term treatment or relapse prevention data for alpha-2 delta ligands.

The only other antiepileptic drug assessed in RCT is levetiracetam, which has a complex pharmacology.<sup>70</sup> A large trial against placebo was negative.<sup>76</sup> The dose achieved in this trial (1180 mg/day) was at the low end of the dose range for epilepsy (1000–3000 mg/day). However, an earlier small RCT, in which higher levetiracetam doses were achieved, was also negative.<sup>31</sup>

Open-label trials of valproate,<sup>77</sup> topiramate,<sup>78</sup> and tiagabine<sup>79</sup> have also been reported, all of which showed reductions in relevant social phobia rating scales. All studies were small (involving 17–54 subjects), and the magnitude of the change in symptom ratings was within the range that has been reported for placebo arms in other RCT.

### Benzodiazepines

In clinical practice, there appears to be widespread use of benzodiazepines alone or in combination with antidepressants for social phobia,<sup>80,81</sup> but clinical evidence to support this use is relatively limited. There are three placebo-controlled RCT, one each for clonazepam,<sup>82</sup> bromazepam,<sup>83</sup> and alprazolam.<sup>53</sup> All studies showed significantly greater improvement on a range of clinician-rating and self-rating scales compared with placebo. The mean doses used in these studies were generally modest (clonazepam 2.4 mg/day, bromazepam 21 mg/day,

alprazolam 4.2 mg/day). The time course of response was only reported for the clonazepam study. Although there was a higher proportion of responders after one week of treatment (clonazepam 13.5%, placebo 0%), maximal response rates were noted after 6 weeks of treatment. Continuation of clonazepam treatment in treatment responders has been shown to decrease rates of relapse in social phobia compared with those switched to placebo.<sup>84</sup>

Although the clinical practice of combining antidepressants and benzodiazepines appears to be common, it has been studied in only one small RCT. Combined paroxetine and clonazepam had a higher response rate (albeit not a statistically significant one) in an RCT in social phobia (79% versus 43%,  $P = 0.06$ ) compared with paroxetine plus placebo.<sup>85</sup>

### Antipsychotics

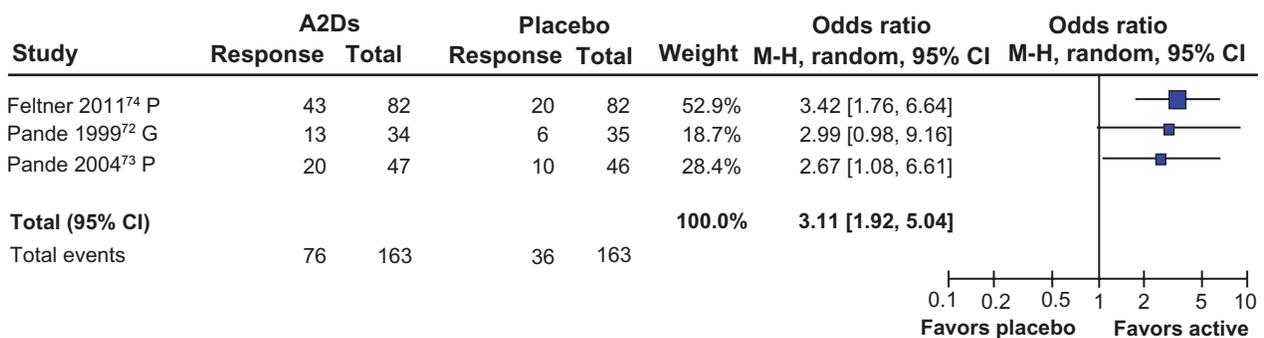
Increased use of second-generation antipsychotic drugs for anxiety disorders has been identified in US prescribing data between 1996 and 2007.<sup>86</sup> The evidence base to support use in social phobia is very limited, with two small RCT. CGI response rates were not statistically significantly different between placebo and olanzapine<sup>87</sup> or quetiapine,<sup>88</sup> although the very small subject numbers ( $n = 7–10$  subjects on active medication) suggest that neither trial was adequately powered statistically.

### Other agents

Negative RCT outcomes have been reported for buspirone, a serotonin 1A partial agonist,<sup>89</sup> and for atenolol, a beta-adrenoceptor antagonist.<sup>89</sup>

### Summary of medication response

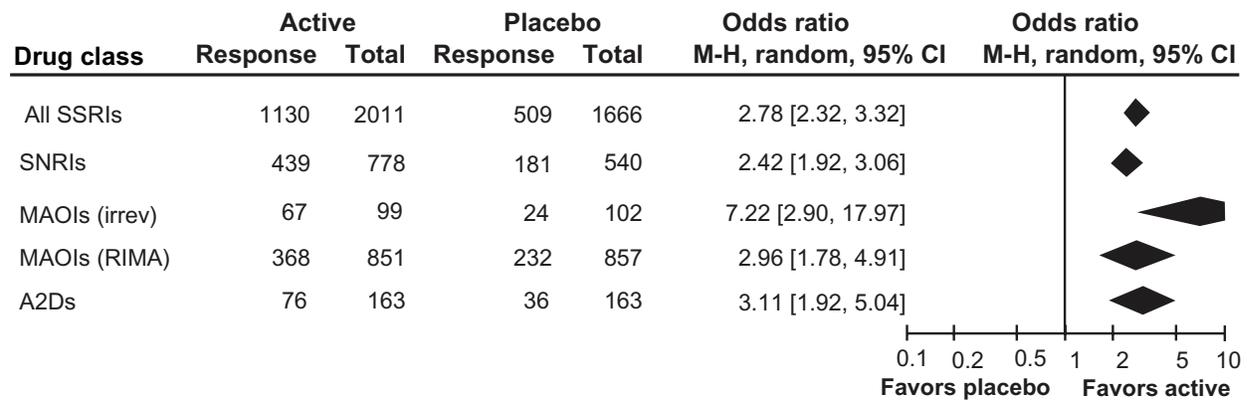
Placebo-controlled RCT have been reported for seven drug classes in social phobia. Figure 5 shows the comparative OR



**Figure 4** Odds ratios and 95% CI for treatment response in randomized placebo-controlled trials for the A2D ligands pregabalin (P) and gabapentin (G).

Response based on CGI for all studies. Only the highest pregabalin doses are reported for Pande et al<sup>73</sup> and Feltner et al.<sup>74</sup>

**Abbreviations:** A2D, alpha-2-delta; CI, confidence interval; M-H, Mantel-Haenszel odds ratio.



**Figure 5** Odds ratios and 95% CI for treatment response in randomized placebo-controlled trials for five drug classes.

**Abbreviations:** CI, confidence interval; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; MAOIs, monoamine oxidase inhibitors; irrev, irreversible; RIMA, selective inhibitors of monoamine oxidase A; M-H, Mantel-Haenszel odds ratio.

for treatment response for pooled results from five of these classes (insufficient data were available to include antipsychotic and benzodiazepine class data). The greatest treatment response was for the irreversible nonselective monoamine oxidase inhibitor, phenelzine. It should be noted that this estimate is heavily influenced by data from one study,<sup>50</sup> and that relatively few patients were included in the four studies. Because of the risk of food and drug interactions, use of this class of drugs would not be first-line. The OR for reversible selective inhibitors of monoamine oxidase A is influenced by brofaromine data; brofaromine is not available to prescribe, and responses for moclobemide alone are more modest (OR 1.95; 95% CI 1.37–2.79). The other three drug classes have similar OR for treatment response, suggesting that differences in safety and tolerability profiles might influence selection between drug classes. Efficacy of the alpha-2 delta ligand, pregabalin, has only been reported at the 600 mg dose but not at lower doses; this higher dose is associated with high rates of dizziness and sedation. By default, this leaves SSRIs and the SNRI, venlafaxine, as first-line medication options for treatment of social phobia.

## Psychological treatment trials

Over 30 randomized trials of psychological treatments have been conducted.<sup>15,16</sup> Collectively these indicate that psychological interventions are effective in the treatment of social phobia. A critical issue is, however, effective relative to what? There is great variability in the nature of the control arm in psychological trials. These may include wait-list control, psychological placebo, drug, drug-placebo, or treatment as usual (which may or may not include drugs). Most studies have used wait-list control which is the least stringent test of effectiveness. Recent meta-analyses of psy-

chological treatments have found fairly large effect sizes for psychological treatments compared with wait-list controls (Cohen's *d* of 0.86), but smaller effect sizes (0.36–0.38) compared with placebo or treatment as usual.<sup>15,16</sup>

In addition to the question of whether psychological treatments are effective, a second question is which psychological treatment is optimal. Most studies, especially the earlier ones, have investigated variants or components of cognitive behavior therapy (CBT). The two meta-analyses cited earlier<sup>15,16</sup> conducted subgroup analyses to determine whether inclusion of specific components of CBT, such as exposure, cognitive restructuring, relaxation, and social skills training makes a difference to treatment effectiveness. Neither study found significant differences in effectiveness as a function of inclusion versus noninclusion of any of these treatment components, nor did they find differences according to whether treatment was delivered individually or in group format.

This might suggest that it does not matter which type of psychological treatment is used, but recent trials of CBT against other evidence-based psychological treatments suggest otherwise. Koszycki et al<sup>90</sup> randomized participants with DSM-IV diagnoses of generalized social phobia to either group CBT or mindfulness-based stress reduction. Both groups improved, but the improvement with CBT was significantly greater. Borge et al<sup>91</sup> compared interpersonal therapy with CBT in a randomized trial conducted in a residential setting. Both treatments were equally effective, although the researchers noted that the CBT intervention was associated with less improvement compared with that reported by prior researchers. In a recent randomized controlled trial, Stangier et al<sup>92</sup> compared cognitive therapy with interpersonal psychotherapy. Both treatments were superior

to wait-list control, but cognitive therapy was significantly more effective, a difference that was maintained at one-year follow-up. On the basis of this small number of studies, CBT or some variant of it remains the psychological treatment of choice, but interpersonal therapy or mindfulness-based therapies may be useful alternatives for patients who do not respond to CBT. A further important consideration is whether treatment effects endure. A meta-analysis of nine RCT of variants of CBT found significant effects at post-treatment (Cohen's *d* of 0.68 across all trials) that were maintained at follow-up, with no drop in effect size (0.76).<sup>16</sup>

The availability of psychological treatments such as CBT is often limited by funding or therapist constraints, so recent RCT that have found Internet CBT to be equally effective as the therapist-delivered version are a promising development.<sup>93,94</sup> More research is required to determine whether Internet therapy can be as effective as the therapist-delivered version for the full spectrum of social phobia severity and complexity (in terms of comorbidity).

## Medication versus psychological treatment

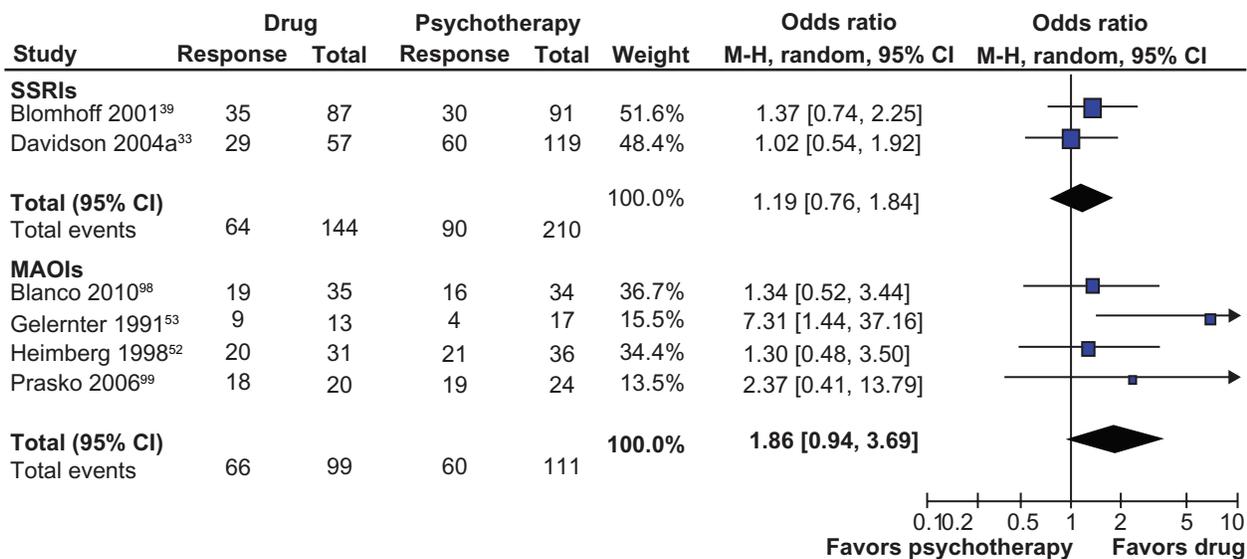
There are relatively few trials incorporating direct comparisons of medication with psychological treatments in social phobia. On the basis of the two trials shown in Figure 6, there are no significant differences in effectiveness between SSRIs and psychological treatments. One additional trial of cognitive therapy versus fluoxetine,<sup>95</sup> which could not be

included in the meta-analysis because the outcome analysis did not include responder data, found a significantly greater effectiveness of cognitive therapy. The meta-analysis of four monoamine oxidase inhibitor trials (Figure 6) suggests that these drugs may be superior to psychological treatments, but this result is not statistically significant.

It is also important to consider how these treatments compare over the longer term. Three studies<sup>95-97</sup> have published follow-up data on outcomes after a treatment-free period. In all three trials, the psychological treatment showed greater maintenance of treatment gains or protection against relapse relative to the drug treatments.

## Medication versus combined medication-psychological treatment trials

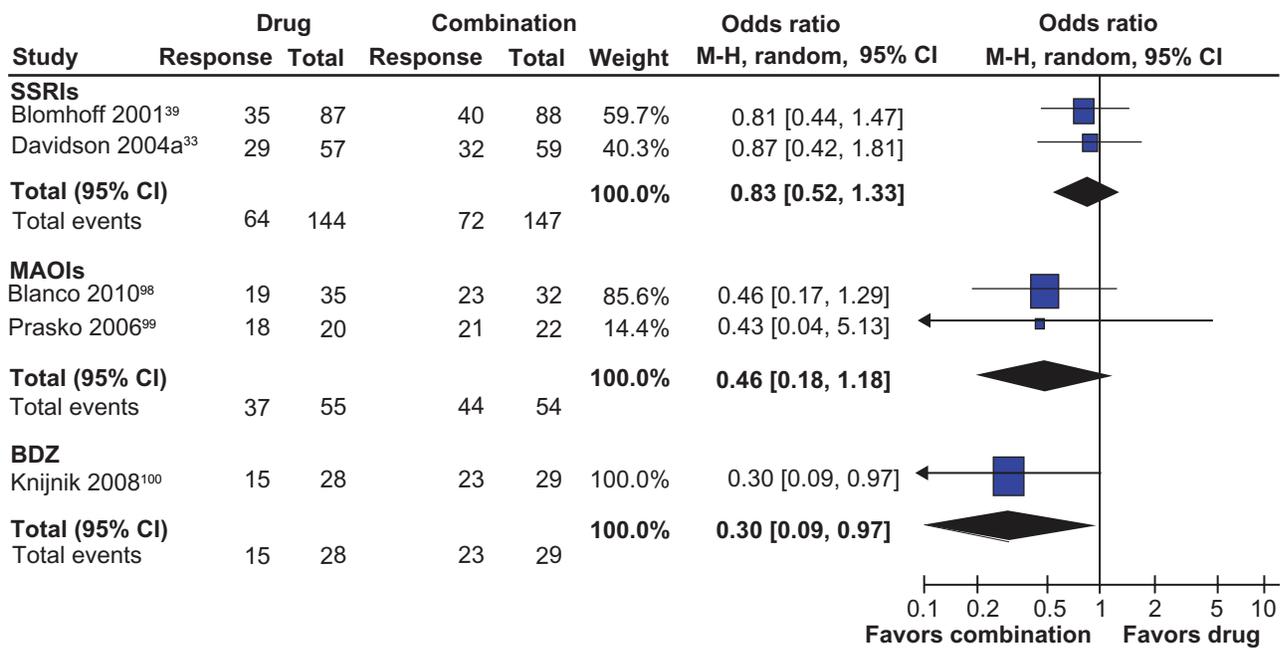
There are five studies that have assessed treatment response in direct comparisons of medication with combined medication-psychological treatments in social phobia (two SSRI studies,<sup>33,39</sup> two monoamine oxidase inhibitor studies,<sup>98,99</sup> and one benzodiazepine study<sup>100</sup> Figure 7). For response rates in the SSRI and monoamine oxidase inhibitor studies, there were nonsignificant trends in favor of combined medication-psychological treatments over medication alone. For the single benzodiazepine study, there was a statistically significant advantage in favor of combined treatment (Figure 7). It should be noted that all studies were relatively small in size and thus may not have been adequately powered statistically.



**Figure 6** Odds ratios and 95% CI for treatment response in randomized placebo-controlled trials for drug versus psychotherapy comparisons.

Blomhoff et al<sup>39</sup> used exposure therapy; all other trials used cognitive behavioral therapy as the psychotherapy intervention. Response based on Clinical Global Impression for all studies except social phobia subscale of the Fear Questionnaire<sup>108</sup> for Gelernter et al,<sup>53</sup> and the Social Anxiety Scale<sup>107</sup> for Heimberg et al.<sup>52</sup>

**Abbreviations:** CI, confidence interval; SSRIs, selective serotonin reuptake inhibitors; MAOIs, monoamine oxidase inhibitors; M-H, Mantel-Haenszel odds ratio.

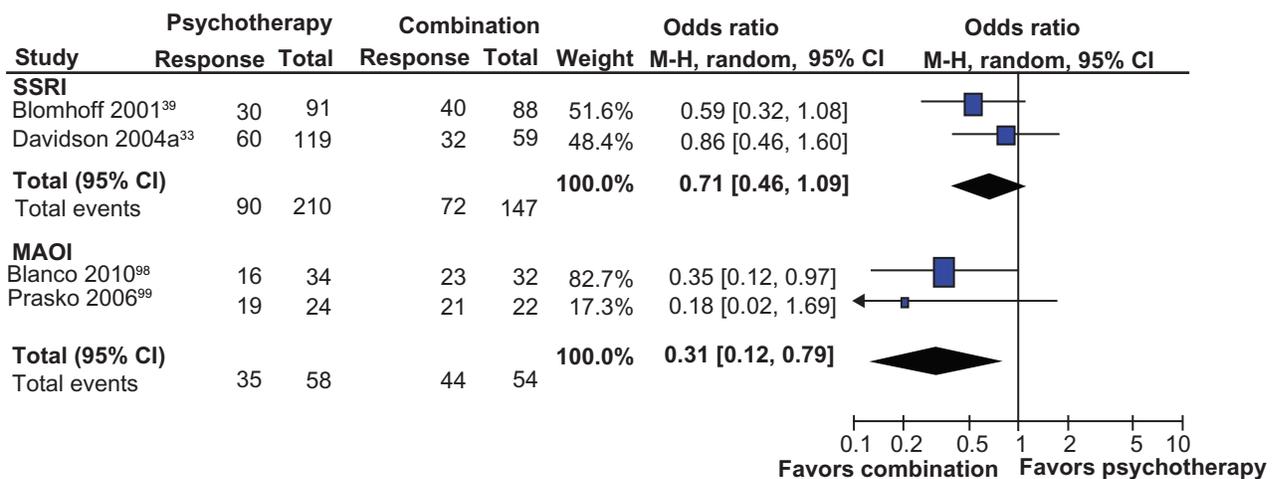


**Figure 7** Odds ratios and 95% CI for treatment response in randomized placebo-controlled trials for medication compared with combined medication-psychological treatment. Blomhoff et al<sup>39</sup> used exposure therapy; Knijnik et al<sup>100</sup> used psychodynamic group therapy; all other trials used cognitive behavioral therapy as the psychotherapy intervention. Response based on Clinical Global Impression for all studies. **Abbreviations:** CI, confidence interval; SSRIs, selective serotonin reuptake inhibitors; MAOIs, monoamine oxidase inhibitors; BDZ, benzodiazepines; M-H, Mantel-Haenszel odds ratio.

### Psychological versus combined medication-psychological treatment trials

There are four studies that have assessed treatment response in direct comparisons of psychological treatment with combined medication-psychological treatments in social phobia (two SSRI studies,<sup>33,39</sup> two monoamine oxidase inhibitor studies<sup>98,99</sup> Figure 8). For the pooled response rate in the SSRI studies, there was a nonsignificant trend

in favor of combined medication-psychological treatments over psychological treatment alone. For the pooled response rate in the monoamine oxidase inhibitor studies, there was a significant trend in favour of combined medication-psychological treatments over psychological treatment alone (Figure 8). It should be noted that all studies were relatively small in size and thus may not have been adequately powered statistically.



**Figure 8** Odds ratios and 95% CI for treatment response in randomized placebo-controlled trials for psychological therapy compared with combined medication-psychological treatment. Blomhoff et al<sup>39</sup> used exposure therapy; all other trials used cognitive behavioral therapy as the psychotherapy intervention. Response based on Clinical Global Impression for all studies. **Abbreviations:** CI, confidence interval; SSRI, selective serotonin reuptake inhibitor; MAOI, monoamine oxidase inhibitor; M-H, Mantel-Haenszel odds ratio.

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## Discussion

All social phobia treatment guidelines recommend some combination of medication and psychological treatment for optimal management of patients with social phobia.<sup>17,18</sup> Our meta-analysis findings are not inconsistent with this, although significant advantages of combination therapies are only evident with some drug classes and from a fairly small number of studies. For medications, the best initial choices would be SNRIs and SSRIs. For patients who do not respond to adequate doses/durations of dosing of either of these drug classes, monoamine oxidase inhibitors would be a relevant second-line choice. The older nonselective irreversible monoamine oxidase inhibitor, phenelzine, is clearly more effective than the newer reversible selective agent, moclobemide, although its use is constrained by its well known food and drug interaction liabilities and side effect profile at higher doses. A number of other drug classes are commonly used for symptom relief in social phobia, and appear to be effective, although clinical trial data are limited. Benzodiazepine use should be limited to brief courses because of their dependence liability, relatively high levels of cognitive toxicity,<sup>102</sup> and potential for interfering with psychological treatment.<sup>103</sup> Low doses of quetiapine are also commonly used for anxiolysis,<sup>104,105</sup> but the one RCT for this drug in social phobia was clearly underpowered to assess its effect.<sup>88</sup> Given that all benzodiazepines and most antipsychotic drugs have now become genericized, there is no commercial rationale for additional RCT in this area, and therefore it is unlikely that additional data will be generated to clarify how best to use these drugs in social phobia. The alpha-2-delta ligand, pregabalin, appears to have anxiolytic response rates comparable with SSRIs and SNRIs, but at doses of 600 mg/day where sedation and other side effects are likely to be reported, so its use should be reserved for refractory patients at this time. Combination drug treatment appears to be commonly used,<sup>80,81</sup> but is not supported by RCT. The issue of how to treat patients who fail to respond to initial treatment is unresolved. A recent clinical guidance suggests a switching strategy, presumably based on data from the STAR\*D studies,<sup>106</sup> but this is not supported by clinical trial data.

Of the psychotherapeutic approaches, CBT or some variant of it appears to be the most effective psychological treatment. It has the largest evidence base, and thus far it has emerged as superior in head-to-head comparisons with other recently developed, evidence-based treatments of mental disorders. CBT also appears to offer better protection from relapse at termination of treatment relative to drug treatments.

## Limitations

Most treatment trials, particularly medication trials, only enroll a highly selected group of patients. Patients with comorbid disorders, such as current depression, alcohol misuse disorders, or suicidal ideation are usually excluded. As noted in the Introduction, comorbidity is the rule rather than the exception for patients with social phobia. Moreover, social phobia has a high degree of overlap with agoraphobia,<sup>101</sup> and can be accompanied by fears of public transport, meaning that some of the most severely affected will not seek treatment. This has implications for the generalizability of the findings reported here.

The effectiveness of combined treatments for social phobia highlights the problem that psychological treatments are not widely available in most countries, and social phobia is one of the most prevalent mental disorders, suggesting significant unmet need for the optimal treatment package for this debilitating disorder. This makes the emerging evidence of the efficacy of Internet-based CBT,<sup>94</sup> at least for uncomplicated presentations, a potentially important new opportunity to maximize the availability of combined treatments.

## Disclosure

Within the last 3 years, JC has received a speaker's honorarium from Novartis Pharmaceuticals, and PG has been on the scientific advisory boards for Forrest Pharmaceuticals, Demerx Pharmaceuticals, and Janssen-Cilag.

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