Published in final edited form as:

Qual Life Res. 2014 May ; 23(4): 1141–1153. doi:10.1007/s11136-013-0573-8.

Effect of Pharmacotherapy for Anxiety Disorders on Quality of Life: A Meta-Analysis

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Abstract

Purpose—Pharmacotherapy is an effective treatment for anxiety disorders, but its effects on quality of life have not been examined systematically. Our objective was to conduct an effect size analysis of pharmacological interventions on quality of life outcomes in patients with DSM-IV anxiety disorders.

Methods—Manual and electronic searches using PubMed, PsycINFO, and the Cochrane Library were conducted for records from the first available date through May 1st, 2013 for trials of pharmacological interventions in patients with anxiety disorders, which had measures of quality of life before and after treatment. Of 1,865 entries, 93 studies were identified as potentially relevant and 32 met inclusion criteria, of which results were examined from 22 studies reporting 27 distinct pharmacological trials, representing data from 4,344 anxiety disorder patients. Data were extracted independently by multiple observers to estimate within-group and placebo-controlled random effects of the treatment changes on quality of life. We hypothesized that pharmacotherapy improves quality of life, which is associated with improvement in anxiety symptoms.

Results—Pharmacological interventions effectively improved quality of life from before to after treatment (Hedges' $g = .59$), although the controlled effect size is smaller among those trials with placebo interventions (Hedges' $g = .32$). These effect sizes were robust, increased with publication year, and increased with reductions in anxiety symptoms.

Conclusions—Pharmacological therapy is effective for improving quality of life in anxiety disorders, and larger symptom reductions are associated with greater improvement in quality of life.

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Critical revision of the manuscript for important intellectual content: Stefan G. Hofmann, Jade Q. Wu, Hannah Boettcher and Jamie Sturm

Statistical analysis: Stefan G. Hofmann, Jade Q. Wu, Hannah Boettcher and Jamie Sturm

Obtained funding: The study is not funded.

Administrative, technical, or material support: Stefan G. Hofmann, Jade Q. Wu, Hannah Boettcher and Jamie Sturm

Study supervision: Stefan G. Hofmann, Jade Q. Wu, Hannah Boettcher and Jamie Sturm

Additional Contributions: The authors would like to thank Meredith Schreier, M.A., Boston University, for her generous assistance with the project. Ms. Schreier received no compensation for her contributions.

Previous Presentations: The study has not been presented.

Keywords

meta-analysis; anxiety; pharmacotherapy; quality of life; psychopharmacology; SSRI

Anxiety disorders are prevalent psychiatric disorders [1] that are associated with high personal and economic costs [2] and low quality of life [3–6] that may be even greater than the influence of chronic medical disorders [7,8]. Quality of life (QOL) refers to subjective well-being, life satisfaction, perceptions of social relationships, physical health, economic status, and functioning in daily activities and work [4,9] and is typically assessed through subjective views of one's life circumstances, perceptions of mental and physical health, social and family relationships, and functioning at work and home [10].

Pharmacotherapy and CBT are commonly used and effective strategies to manage anxiety disorders. While both treatments are associated with decreased symptom severity, it has been argued that QOL should also be considered for examining treatment efficacy [11, 12]. However, there are currently no systematic reviews of QOL outcomes from clinical trials for the treatment of anxiety disorders. In the present meta-analysis, we aim to address this gap, focusing on QOL changes in anxiety disorders produced by pharmacotherapy trials.

The aim of this study was to conduct an effect size analysis of pharmacotherapy on QOL in patients with anxiety disorders, including panic disorder, agoraphobia, social anxiety disorder, generalized anxiety disorder, obsessive compulsive disorder, and posttraumatic stress disorder. We hypothesized that pharmacotherapy is a robust and effective method to enhance QOL of individuals with anxiety disorders.

Methods

Searching

We conducted a systematic search on May 1, 2013 in PubMed, PsycINFO, and the Cochrane Library for all available studies (the earliest of which dated from 1981). The following three sets of search terms were used simultaneously: 1) *quality of life* or *quality-of-life*; 2) pharmacotherapy OR pharmacology OR psychopharmacotherapy OR psychopharmacology OR psychotropic OR drug OR medication OR antidepressant OR SSRI OR tricyclic OR MAOI; and 3) *anxiety* or *anxious* or *panic* or *agoraphobia* or *social phobia* or *social anxiety* or *SAD* or *generalized anxiety* or *GAD* or *obsessive compulsive* or *obsessive-compulsive* or *OCD* or *specific phobia* or *simple phobia* or *post-traumatic stress* or *posttraumatic stress* or *PTSD* or *acute stress* or *ASD*. In addition, manual searches for potentially relevant studies were conducted via reference lists of papers identified through systematic database searches; however, no papers identified through manual searches ultimately met all inclusion criteria, so they were not included in the meta-analysis.

Selection

Studies were selected by two of the authors (HB and QJW) and three independent trained assessors. Studies were included in the present meta-analysis if they met all of the following criteria: 1) they included at least one pharmacological intervention, and this was the primary treatment (i.e. not adjunctive to cognitive-behavioral therapy); 2) the patient sample was diagnosed with one or more anxiety disorders; 3) the patient sample was adult (i.e. 18 years of age or older); 4) they administered at least one measure of QOL at pre- and post-treatment; 5) they provided sufficient data for performing effect size calculations. Consensus regarding a study's inclusion qualification was reached among all authors through case-by-case discussion if there was disagreement.

Studies were excluded if: 1) we were unable to obtain their full text or full English translation; 2) the sample was not human or was not adult; 3) the study did not include a pharmacological intervention; 4) the principal diagnosis of the sample was not an anxiety disorder; 5) the study was not an empirical investigation (i.e., it was a qualitative study or a review paper), or was a meta-analysis; 6) the study did not use a QOL measure; or 7) the study did not provide sufficient data for calculating effect sizes, and we were unable to obtain these data from the authors. In the event that multiple studies reported data from the same trial, the study with the more comprehensive QOL data was chosen.

Validity Assessment

The following modified Jadad criteria [13] were used by three of the authors (QJW, HB and JS) and three independent trained assessors to determine study quality: (1) the study was described as randomized; (2) participants were adequately randomized; (3) the study was described as double blind; (4) the method of double blinding was appropriate; and (5) a description of drop-outs and withdrawals was provided. One point was assigned for each criterion met. One point was deducted from the study quality score in each of the following scenarios: (1) randomization was conducted inappropriately; and (2) the study was described as double blind but the blinding was conducted inappropriately. A Jadad score of zero is possible if either the study in question meets none of the criteria for point addition or if certain limitations of the study resulted in point subtraction. Inter-rater agreement regarding study quality ratings between one trained assessor and one author (JS) was calculated as a weighted kappa coefficient of .62, which is considered a good strength of agreement [14]. Consensus for cases where there was disagreement was reached through discussion between authors.

In order to address potential publication bias, we conducted a fail-safe N analysis [15, 16]. The fail-safe N represents the number of studies needed to nullify the calculated effect size, where a value of $5K + 10$ is considered to be robust when K is the number of studies in the pooled analysis. Although fail-safe N analyses are commonly reported in meta-analyses, including some of our own [17], this methodology is not without controversy because of its over-emphasis on statistical significance, among other problems [23]. Therefore, we also constructed a funnel plot to assess publication bias. The Trim and Fill method, which takes into account the sample size of the studies, was used to judge whether negative or positive trials were under- or overrepresented.

Data Extraction

Two of the authors (HB and QJW) selected psychometrically validated measures of QOL and anxiety symptoms reported in selected studies and extracted their numerical data. These data were then used to compute effect sizes for pre- to post-treatment changes. In cases in which necessary data was not reported in the published study, we contacted corresponding authors to request the relevant data.

Study Characteristics—Information about drug type, drug dosing, patient characteristics, outcome measures used and other study characteristics was also extracted (see Table 1). Twenty-seven trials were identified. Among those, the following drug types were used: Selective serotonin reuptake inhibitors (SSRI; 17 trials), Serotonin-norepinephrine reuptake inhibitors (SNRI; 6 trials), serotonin-norepinephrine-dopamine reuptake inhibitors (SNDRI; 1 trial) noradrenergic and specific serotonergic antidepressants (NaSSA; 1 trial), and antipsychotics (2 trials).

Quantitative Data Synthesis

To evaluate improvements in QOL and anxiety symptoms, we computed pooled Hedges' g and its 95% confidence interval [19]. Hedges' g is a version of Cohen's d modified to account for sample size bias. We used the following formula to calculate within-group pre-

post effect sizes: $d = \left(\frac{\bar{Y}_1 - \bar{Y}_2}{S_{\text{Difference}}} \right) \sqrt{2(1-r)}$, where $\bar{Y}_1$ is the pre-treatment sample mean, $\bar{Y}_2$ is the post-treatment sample mean, $S_{\text{Difference}}$ is the standard deviation of the difference, and r is the correlation between pre-treatment and post-treatment scores. Hedges' g can be

computed by multiplying d by correction factor $J(df) = 1 - \frac{3}{4df-1}$, where df is the degrees of freedom used to estimate the within-group standard deviation. The controlled effect sizes were computed using the following formula:

$$g = \frac{\bar{\Delta}_{\text{TREAT}} - \bar{\Delta}_{\text{CONT}}}{\sqrt{\frac{(n_{\text{TREAT}}-1)SD_{\text{CONT}}^2 + (n_{\text{TREAT}}-1)SD_{\text{TREAT}}^2}{(n_{\text{total}}-2)}}} \times \left(1 - \frac{3}{4(n_{\text{TREAT}} + n_{\text{CONT}}) - 9} \right)$$
, where $\bar{\Delta}$ is the mean pre- to post-treatment change, SD is the standard deviation of post-treatment scores, n is the sample size, TREAT refers to the pharmacological therapy condition, and CONT refers to the placebo group.

Consistent with Cohen [20], we interpret this effect as small (0.2), medium (0.5) or large (0.8). In trials with multiple measures of QOL or anxiety symptoms, we averaged effect size estimates across all measures.

Pre-post correlations are necessary for computing effect sizes. We used a conservative estimate of $r = .70$ in the event that the correlation was not reported, following Rosenthal's recommendation [21]. We favored the random-effects model over fixed-effects due to differences among included trials [22,23].

Moderator Analyses

In order to examine potential moderators, we analyzed whether the QOL outcome varied according to study characteristics (study year, study quality, type of medication), and patient characteristics (diagnostic category, extent of anxiety symptom change). For categorical moderators (e.g., anxiety diagnosis), we computed separate effect sizes for each group. We used meta-regression analyses for continuous moderators (e.g., study year). All analyses were conducted using the program Comprehensive Meta-Analysis, Version 2 [24].

Results

Trial Flow

The study search and selection process is shown in Figure 1. Our initial search returned 1,865 hits, the majority of which did not meet inclusion criteria. 32 studies met the inclusion criteria. Of these, 10 studies were excluded because of incomplete data. Twenty-two published studies [25–46] met all inclusion criteria and had sufficient data for conducting effect size analyses. Five studies included multiple separate drug conditions, so that a total of ten trials from these studies were analyzed as distinct trials [25, 38, 43–44, 46]. This resulted in a total of 27 trials included in this meta-analysis. Taken together, there were data for 4,344 patients across all trials. The disorders included generalized anxiety disorder (7 trials), posttraumatic stress disorder (6), obsessive compulsive disorder (5), panic disorder (5), and social anxiety disorder (4). Table 1 lists the detailed information on study characteristics.

Study Characteristics—We used modified Jadad criteria [14] to evaluate the quality of included trials. Jadad scores ranged from 0 to 5 ($M = 2.40$, $SD = 1.63$). Details of study characteristics are summarized in Table 1.

The QOL measures used in the studies included: Quality of Life Inventory [47], World Health Organization Quality of Life Assessment [48], Quality of Life Enjoyment and Satisfaction Questionnaire [49], Sheehan Disability Scale [50], MOS 36-item short-form health survey [51,52], the Medical Outcomes Study short form self-report health survey [53] and the Lancashire Quality of Life Profile [54].

These instruments are self-report measures of QOL with good psychometric properties and a history of use in clinical populations. Table 2 enlists studies in which the psychometric properties of these measures were established among anxiety disorder populations. Among the many QOL domains accessed are physical health, psychological health, social relationships, role functioning, occupational involvement, and overall sense of well-being. We were unable to report synthesized QOL outcomes by specific domain due to the diversity of QOL measures across studies. Moreover, many studies did not report individual domain scores on instruments with multiple domains. Thus, our analyses were limited to overall QOL outcomes.

Quantitative Data Synthesis

Pre-post within-group treatment effect on quality of life—The pooled Hedges' g was 0.59 (95% CI : 0.44–0.74, $z = 7.71$, $p < .0001$). At $p < .01$, the fail-safe N was 1,532 ($z = 19.57$), indicating that 1,532 studies finding no effect on QOL would be necessary to negate this finding. Table 3 shows the effect size estimates by individual study, grouped by disorder.

All but two trials used drugs of the antidepressant type. Therefore, we also computed pre-post within-group random effect sizes for QOL improvement without the two trials using antipsychotics. With the antipsychotic trials removed, we again obtained a moderately strong effect size, similar to that obtained using all trials (Hedges' $g = .60$, 95% $CI = .44-.75$, $z = 7.48$, $p < .001$).

The funnel plot is presented in Figure 2. A Trim and Fill analysis indicated that the plot would require 7 studies to the right of the mean and 0 studies to the left of the mean in order to be symmetrical. The imputed effect size estimate for improvements in QOL was Hedges' $g = 0.79$ (95% CI : 0.58–0.99).

Pre-post controlled treatment effect on quality of life. Ten of the trials (extracted from 9 studies) included a placebo control and were included in the present controlled treatment effect analysis. This analysis includes only those trials with both pharmacological intervention and a placebo intervention. Thus, it does not include the 4 studies that had pharmacological comparison groups, but no placebo control (e.g., Ball et al., 2005, which compared paroxetine and sertraline). These studies constituted a total of 8 distinct trials in our pre-post within-group analyses.

Among the ten placebo-controlled trials, we obtained a QOL controlled effect size of Hedges' $g = 0.32$ (95% CI : 0.22–0.43, $z = 5.99$, $p < .0001$). At $\alpha = .01$, the fail-safe N for measures of QOL was 96 ($z = 2.58$), indicating that 96 controlled studies with an effect size of zero would be needed to negate the controlled effect size results.

Treatment effect on anxiety—All but three of the trials provided useable data on the effects of the pharmacological intervention on anxiety symptoms. The pre-post within-group

random effect size on anxiety symptoms was Hedges' $g = 1.17$ (95% CI : 0.85–1.48, $z = 7.23$, $p < .0001$). At $p < .01$, the fail-safe N for measures of anxiety was 3,195 ($z = 29.83$).

The Trim and Fill funnel plot indicated that 0 studies would need to fall to the left of the mean effect size and 4 studies would need to fall to the right of the mean in order to achieve symmetry. The imputed effect size for anxiety symptom improvement: was Hedges' $g = 1.40$ (95% CI : 1.02–1.79).

The controlled effect size of anxiety symptoms was Hedges' $g = 0.45$ (95% CI : 0.15–0.74, $z = 2.94$, $p < .01$). At $p < .01$, the fail-safe N for measures of anxiety was 51 ($z = 6.99$), indicating that 51 controlled studies with an effect size of zero would be needed to negate the reported results. A Trim and Fill analysis showed that 0 studies would need to fall to the left of the mean effect size and 3 studies would need to fall to the right of the mean effect size to make the funnel plot symmetrical. The imputed controlled effect size for improvement in anxiety symptoms using a random-effects model was Hedges' $g = 0.74$ (95% CI : 0.36–1.13).

Moderator analyses—The diagnosis-specific effect sizes on QOL ranged from medium to large for generalized anxiety disorder (Hedges' $g = 1.26$, 95% CI : 0.54–1.98, $z = 3.45$, $p = .001$), post-traumatic stress disorder (Hedges' $g = 0.42$, 95% CI : 0.24–0.61, $z = 4.43$, $p < .0001$), obsessive compulsive disorder (Hedges' $g = 0.31$, 95% CI : 0.04–0.58, $z = 2.27$, $p = 0.23$), panic disorder (Hedges' $g = 0.39$, 95% CI : 0.21–0.57, $z = 4.30$, $p < .001$) and social anxiety disorder (Hedges' $g = 0.41$, 95% CI : 0.18–0.64, $z = 3.51$, $p < .001$). For GAD, the large effect size was driven by one particular study comprising two trials of citalopram and venlafaxine for generalized anxiety disorder (Zhang et al., 2013; Hedges' $g = 3.35$, Hedges' $g = 2.16$). For comparison, removing these two trials reduces the effect size on QOL in GAD (Hedges' $g = .54$, 95% CI : 0.36–.72, $z = 5.80$, $p < .0001$).

QOL life effect sizes were moderated by publication year ($B = 0.03$, $SE = 0.01$, $p < .0001$), indicating that the effect sizes increased linearly with time. We also found a negative relationship between study quality, as assessed by Jadad scoring, and improvements in QOL ($B = -0.06$, $SE = 0.02$, $p < .001$). Finally, improvement in QOL was significantly associated with improvement in anxiety symptoms ($B = 0.49$, $SE = 0.08$, $p < .0001$).

Only trials using SSRIs and SNRIs were sufficiently numerous for calculating a meaningful pooled effect size. The pre-post within-group random effect size on QOL was moderately strong for SSRIs (Hedges' $g = .48$, 95% $CI = .32$ –.64, $z = 5.87$, $p < .0001$). The pre-post within-group random effect size on QOL for SNRIs was large (Hedges' $g = .89$, 95% $CI = .40$ –1.39, $z = 3.53$, $p < .0001$), but not significantly stronger than for SSRIs.

Discussion

Anxiety disorders are associated with a low QOL [3–6]. The goal of this study was to examine the effects of pharmacological treatments on QOL in individuals with anxiety disorders.

Our literature search identified 22 studies reporting 27 clinical trials that were based on 4,344 anxiety disorder patients. Most of these studies examined selective serotonin reuptake inhibitors (17 trials) and serotonin-norepinephrine reuptake inhibitors (6 trials). The pooled Hedges' g of the pre-post effect size of pharmacotherapy on QOL was 0.59 (95% CI : 0.44–0.74, $z = 7.71$, $p < .0001$). The fail-safe N ($N = 1,532$) and Trim and Fill analysis of the funnel plot (corrected Hedges' $g = 0.79$) suggests that the effect size estimate was robust. As expected, the placebo-controlled effect size estimate was lower (Hedges' $g = 0.32$, but still

remained robust as suggested by the fail-safe N analysis ($N = 96$) and Trim and Fill method (corrected Hedges' $g = 0.74$).

These results suggest that pharmacological interventions effectively improve QOL in patients with anxiety disorders. The beneficial effect of pharmacotherapy on QOL was stronger for generalized anxiety disorder than for the other anxiety disorders. However, this effect should be interpreted with caution because this finding might have been due to 2 clinical trials that reported very strong effects of pharmacotherapy on improvement of QOL in patients with generalized anxiety disorder. This is in line with a previous review showing that no anxiety disorder is associated with significantly poorer QOL than any other anxiety disorder [5]. It should be further noted that a direct comparison between the treatment effects on QOL for anxiety disorders is problematic because of differences in comorbidities and disease characteristics, and possibly differential specificity of the QOL assessment instrument for the various disorders. For example, it may be possible that patients who experienced a very early disease onset defined the impact of the symptoms on QOL differently than individuals who initially had a high QOL, which then dramatically changed after the disease onset [6]. However, except for a publication year effect, our moderator analyses showed no indication of a systematic bias in the results. For example, QOL outcome did not vary according to study characteristics (study quality and type of medication) or patient characteristics (diagnostic category and extent of anxiety symptom change).

There was also no difference in the effects on QOL across different types of medication. However, there were only enough studies to examine the effects of SSRIs and SNRIs separately. Additional moderator analyses revealed that the treatment effect on QOL increased with publication year. This phenomenon, in which replications of research decline in significance over time, has been termed “cosmic habituation,” as well as the “decline effect,” [60,61]. This effect has been observed both within psychology and in other fields of study, and is therefore not unique to our findings. Since study quality did not moderate treatment effect, it is unlikely that differences in study quality are responsible for this effect.

Treatment effects were also negatively associated with study quality, which may suggest that uncontrolled effect sizes tended to be higher than those for placebo-controlled trials. As expected, pharmacotherapy also improved anxiety symptoms, and larger improvements in anxiety symptoms were associated with greater improvements in QOL. This may suggest that improvements in QOL are a function of symptom improvement. Although this is a plausible explanation, the nature of this review is unable to test this causal link.

The results of the study are limited by the nature of the QOL construct. Although each of the QOL measures is commonly used and psychometrically sound, the assessment of QOL was limited to only patient reported outcome. Adding observer reported outcome and clinician-reported outcome assessments [62] might have provided a broader perspective for the assessment of the construct. Furthermore, we were unable to examine the specific QOL domains because studies rarely provided this level of detail. We recommend that future studies examine the individual domains of QOL, including physical health, mental health, social activities, work, home, and family [5]. For example, it is possible that pharmacotherapy for social anxiety disorder primarily enhances the patient's QOL by improving his or her social relationships, whereas treatment for agoraphobia might affect mobility and certain areas of work by targeting agoraphobic avoidance. In addition, CBT is a more cost-effective approach compared to pharmacotherapy, and some countries, such as the UK, have begun to implement policies to widely disseminate CBT [63]. While CBT has been shown to enhance quality of life in various anxiety disorders [64–66], there is still a clear need for an evidence-based approach to treating anxiety disorders emphasizing quality

of life. Finally, it would be important to directly compare the effects of different treatment modalities (psychotherapy vs. pharmacotherapy) on QOL for different patient populations.

Despite these limitations, the results of our review suggest that pharmacotherapy is not only an effective treatment for reducing the immediate symptoms of anxiety disorders, but it also has a beneficial effect on quality of life.

Acknowledgments

Financial Disclosures: Dr. Hofmann reported receiving royalties from multiple publishers. Ms. Wu, Boettcher and Sturm have no financial disclosures to make.

Funding/Support and Role of the sponsor: This study is not supported by any funding agencies.

Financial disclosures: Dr. Hofmann received royalties from multiple publishers. Ms. Boettcher, Ms. Wu and Ms. Sturm have no financial disclosures to make.

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Figure 1.
Study Selection

Figure 2.
Funnel plot of precision by pooled Hedges' g for QOL measures

Study Characteristics

Table 1

Study	Disorders	Drug Therapy	Jadad Score	Sample Size ^a	Dosage (mg/day)	Fixed or Flexible Dosing	Duration (weeks)	% Female	Mean age (SD)	Comorbid diagnoses	% Dropout	Main outcome (Hedge's g)	Placebo Control	QOL Measures	Anxiety Measures
Bull et al., 2005	GAD	Paroxetine, Sertraline	4	53	10-40 (paroxetine); 25-100 (sertraline)	Flexible	8	77%	39.46	Social Anxiety: 5.7% Panic Disorder: 1.9% Depression/dysthymia: 30.2%	22%	Paroxetine: 0.73 Sertraline: 0.68	No	Q-LES-Q	BAI, HAM-A, IU-GAMS
Beisiroglu et al., 2008	OCD	Various SSRIs (pooled data)	1	53	Up to 300	Flexible	12	75%	32.7 (12.2)	MDD: 41.6% Bipolar Disorder: 2.7% GAMS Dysthymic Disorder: 13.8% Panic Disorder: 13.8% GAD: 22.2% Social Phobia: 16.7% Simple Phobia: 22.2% PTSD: 11.1% BDD: 3.5%	32%	0.22	No	WHOQOL-BREF	YBOCS
Blank et al., 2006	GAD	Citalopram	1	30	10-40	Flexible	32	63%	69 (6)	Unknown	43%	1.09	No	SF-36 Mental, SF-36 Physical	HAM-A
Blaya et al., 2007	PD	Minapracin	1	28	50-100	Flexible	10	67.7%	37 (12)	Most comorbidities excluded	24.3%	0.62	No	WHOQOL-BREF	PDSS, HAM-A
Brady et al., 2000	PTSD	Sertraline	0	183	50-200	Flexible	12	73%	39.85	MDD: 33.2% Anxiety Disorder: 16%	2.1%	0.55	Yes	Q-LES-Q	CAPS-2, Davidson PTSD Scale, Impact of Event Scale
Bruce et al., 2012	SAD	Paroxetine	0	127	10-50	Flexible	12	41.9%	32.5 (12)	Unknown	24.4%	0.49	No	QOLI	LSAS
Davidson et al., 2005	PTSD	Escitalopram	2	521	10-20	Flexible	24	53.6%	39.8 (12.8)	Most comorbidities excluded	43.2%	0.24	No	Q-LES-Q	HAM-A
Davidson et al., 2006	PTSD	Venlafaxine	5	329	27.5-300	Flexible	24	54.1%	41.3	Most comorbidities excluded; anxiety comorbidities unknown	31.9%	0.31	Yes	Q-LES-Q-SF	CAPS-SX
Dougherty et al., 2009	OCD	Escitalopram	1	23	20-30	Flexible	16	33.4%	36.7 (12.5)	Current: GAD: 33.4% Social Phobia: 25.9% Specific Phobia: 11.2% Panic Disorder: 3.7% Anxiety Disorder NOS: 3.7% Bulimia: 3.7% MDD: 18.5% Dysthymia: 7.4% Lifetime: MDD: 25.9% Alcohol Abuse: 33.4% Substance Abuse: 3.7% Panic Disorder: 11.2% Anorexia: 3.7% Binge Eating Disorder: 3.7%	14.8%	0.96	No	Q-LES-Q	YBOCS, BAI
Francois et al., 2008	SAD	Citalopram	4	351	10-20	Flexible	24	49%	37	Comorbidities excluded	11%	0.08	Yes	SF-6D	LSAS
Koran et al., 2010	OCD	Fluvoxamine	4	115	100-300	Flexible	52	63.6%	37.4	Any other current primary comorbid diagnosis excluded	Unknown	0.23	Yes	SF-36	Y-BOCS
Krysal et al., 2011	PTSD	Risperidone	4	247	Up to 4	Flexible	24	3.4%	54.4 (10.7)	Alcohol Abuse: 19.1% Alcohol Dependence: 43.4% Cannabis Abuse: 13.1% Cocaine Abuse: 11.2% Cocaine Abuse: 7.5% Dependence: 10.5% MDD: 69.7% Dysthymia: 10.1%	18.2%	0.19	Yes	SF-36	HAM-A

Study	Disorders	Drug Therapy	Jadad Score	Sample Size *	Dosage (mg/day)	Fixed or Flexible Dosing	Duration (weeks)	% Female	Mean age (SD)	Comorbid diagnoses	% Dropout	Main outcome (Hedge's g)	Placebo Control	QOL Measures	Anxiety Measures
										GAD: 10.1% Social Phobia: 3.4% ASPD: 6%					
Liebowitz et al., 2003	SAD	Sertraline	4	401	25–200	Flexible	12	40.5%	35.1	Comorbidities excluded	3.4%	0.39	Yes	Q-LES-Q	LSAS, HAM-A
McRae et al., 2004	PTSD	Nefazodone, Sertraline	4	26	Up to 600 (nefazodone); up to 200 (sertraline)	Flexible	12	76.9%	40.3	Most comorbidities excluded	37.8%	Nefazodone: 0.94; Sertraline: 0.84	No	SDS	HAM-A, CAPS, Davidson Trauma
Merza et al., 2007	GAD	Aripiprazole	1	8	10	Fixed	6	66.7%	35	Secondary Depression diagnosis: 88.9%	11.2%	1.52	No	SF-36	HAM-A
Muehlbacher et al., 2005	SAD	Mirtazapine	4	66	30	Fixed	10	100%	24	Personality Disorder: 25.8% GAD: 45.5% Panic Disorder: 21.2% OCD: 7.6% Alcohol/Drug Misuse: 22.7%	10.6%	0.09	Yes	SF-36	SPIN, LSAS
Pollack et al., 2008	GAD	Duloxetine	3	1163	60–120	Flexible	10	65%	42.2	Comorbidities excluded	Unknown	0.43	Yes	EQ-5D, Q-LES-Q-SF, SDS ^d	HAM-A
Simon et al., 2009	PD	Duloxetine	1	15	60–120	Flexible	8	60%	41.1(15)	MDD: 13.3% Dysthymia: 20% Agoraphobia: 40% Social Anxiety Disorder: 13.3% Specific Phobia: 6.67% GAD: 20%	29.4%	0.69	No	Q-LES-Q	BAI, PDSS, PAS
Stahl et al., 2003	PD	Escitalopram, Citalopram	4	351	10–20 (escitalopram); 20–40 (citalopram)	Flexible	10	58.1%	41	Agoraphobia: 68% Most comorbidities excluded	32%	Escitalopram.: 0.28; Citalopram: 0.21	Yes	Q-LES-Q	HAM-A, PAS
Tenney et al., 2003	OCD	Paroxetine, Venlafaxine	4	101	Up to 60 (paroxetine); Up to 300 (venlafaxine)	Flexible	12	63.7%	36 (12)	Comorbidities excluded	32.7%	Paroxetine: 0.29; Venlafaxine: 0.29	No	LQoLP	YBOCS, HAM-A
van Apeldoorn et al., 2010	PD	Various SSRIs (pooled analysis)	3	53	10–50	Flexible	52	54.7%	37.5 (10.6)	Comorbid Axis I disorder: 50%	Who 37.3%	−0.08	No	RAND-36	HAM-A
Zhang et al., 2013	GAD	Citalopram, Venlafaxine	0	100	75–100	Flexible	12	58%	44.3 (11.3)	Comorbidities excluded	Unknown	Citalopram: 2.16; Venlafaxine: 3.35	No	SF-36	HAM-A

Note. Across the 22 studies described here, there were 27 distinct drug trials.

Disorders: ASPD = antisocial personality disorder; BDD = body dysmorphic disorder; GAD = generalized anxiety disorder; MDD = major depressive disorder; NOS = not otherwise specified; OCD = obsessive compulsive disorder; PD = panic disorder; PTSD = posttraumatic stress disorder; SAD = social anxiety disorder. **Drug Therapy:** SSRIs = selective serotonin reuptake inhibitors. **Jadad Score:** Quality scores based on Jadad et al. (1996) ranging 0 to 5. **QOL measures:** EQ-5D = EuroQol⁵¹; Q-LES-Q = Quality Of Life Enjoyment And Satisfaction Questionnaire⁴⁹; Q-LES-Q-SF = Short Form of the Quality Of Life Enjoyment And Satisfaction Questionnaire⁴⁹; QOLI = Quality Of Life Inventory⁴⁷; RAND-36 = Medical Outcomes Study short form self-report health survey⁵⁴; SDS = Sheehan Disability Scale⁵⁰; SF-36 = MOS 36-item short-form health survey⁵³; WHOQOL-BREF = World Health Organization Quality of Life Assessment⁴⁸; LQoLP = Lancashire Quality of Life Profile⁵⁵ **Anxiety measures:** BAI = Beck Anxiety Index; CAPS = Clinician-Administered PTSD Scale; CAPS-2 = Clinician-Administered PTSD Scale – One-week Symptoms; CAPS-SX = Clinician-Administered PTSD Scale – One-week Symptoms; HAM-A = Hamilton Rating Scale for Anxiety; IU-GAMS = Indiana University Generalized Anxiety Measurement Scale; LSAS = Liebowitz Social Anxiety Scale; PAS = Panic and Agoraphobia Scale; PDSS = Panic Disorder Severity Scale; SPIN = Social Phobia Inventory; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

* Sample size reflects the total *N* used for effect size analyses. This includes all active drug interventions and the placebo control group if applicable, and does not include participants for whom data was incomplete (e.g., dropouts).

^d trials in which effect sizes were averaged across were averaged across all QOL measures

Table 2

Psychometric properties of QOL measures in anxiety populations

QoL Measure (abbreviation)	QoL Measure (full name)	Assessment of Psychometric Properties in Anxiety Disorder Populations	Validated In:
EQ-5D	EuroQol	Konig H.H., et al. (2010) [56]	Panic Disorder, GAD, Unspecified Anxiety Disorder
LQOL	Lancashire Quality of Life Profile	Not specifically established in an anxiety population *	
QLESQ	Quality of Life Enjoyment and Satisfaction Questionnaire	Not specifically established in an anxiety population *	
Q-LES-Q-SF	Short-Form Quality of Life Enjoyment and Satisfaction Questionnaire	Wyrwich, K., et al. (2009) [57]	GAD
QOLI	The Quality of Life Inventory	McAlinden, N. M., & Oei, T. P. (2006). [58]	Panic Disorder, GAD, PTSD, OCD Social Phobia, Depressive Disorders
RAND 36	RAND 36 Health Status Inventory	Not specifically established in an anxiety population *	
SDS	Sheehan Disability Scale	Hambrick, J. P., et al. (2004) [59]	Social Anxiety Disorder
SF-36	Medical Outcomes Study 36-item Short Form Health Survey	Not specifically established in an anxiety population *	
SF-6D	Six-Dimensions Short Form Health Survey	Not specifically established in an anxiety population *	
WHOQOL-BREF-TR	WHO Quality of Life Measurement Instrument, Short Form, Turkish Version	Not specifically established in an anxiety population *	

* Each of these measures has been used in studies with anxiety populations, but psychometric properties have not been established in an anxiety population

Table 3

Hedges' *g* for treatment effects on QOL, by individual drug trials.

Disorder	Study Name	Hedges' <i>g</i> (95% CI)	Z-Value	p-value
Generalized Anxiety Disorder	Ball et al. (2005) – Paroxetine	.73 (.30–1.16)	3.31	.001
	Ball et al. (2005) – Sertraline	.68 (.28–1.08)	3.31	.001
	Blank et al. (2006) – Citalopram	.40 (–0.01–.81)	1.91	.06
	Menza et al. (2007) – Aripiprazole	1.18 (.33–2.03)	2.71	.056
	Pollack et al. (2008) – Duloxetine	.43 (.28–.58)	5.54	<.001
	Zhang et al. (2013) – Citalopram	2.16 (1.77–2.55)	10.85	<.001
	Zhang et al. (2013) – Venlafaxine	3.35 (2.80–3.90)	11.92	<.001
	<i>Total</i>	1.26 (0.54–1.98)	3.45	.001
Obsessive-Compulsive Disorder	Besiroglu et al. (2008) – Various SSRI	–.03 (–.24–.18)	–.29	.77
	Dougherty et al. (2009) – Escitalopram	.96 (.60–1.34)	5.05	<.001
	Koran et al. (2010) – Fluvoxamine	.16 (–.21–.52)	.84	.40
	Tenney et al. (2010) – Paroxetine	.29 (.07–.51)	2.54	.01
	Tenney et al. (2010) – Venlafaxine	.29 (.08–.50)	2.75	.006
	<i>Total</i>	0.31 (0.04–0.58)	2.27	.023
Panic Disorder	Blaya et al. (2007) – Milnacipran	.69 (.38–1.01)	4.31	<.001
	Simon et al. (2009) – Duloxetine	.64 (.23–1.05)	3.05	.002
	Stahl et al. (2003) – Citalopram	.21 (–.05–.47)	1.56	.119
	Stahl et al. (2003) – Escitalopram	.28 (.03–.54)	2.18	.03
	van Apeldoorn et al. (2010) – Various SSRI	.30 (.09–.52)	2.73	.006
	<i>Total</i>	0.39 (0.21–0.57)	4.30	<.001
Post-traumatic Stress Disorder	Brady et al. (2000) – Sertraline	.55 (.26–.85)	3.67	<.001
	Davidson et al. (2005) – Escitalopram	.24 (.17–.31)	6.97	<.001
	Davidson et al. (2006) – Venlafaxine	.31 (.09–.52)	2.77	.006
	Krytaletal. (2011) – Risperidone	.19 (–.06–.44)	1.49	.135
	McRae et al. (2004) – Nefazodone	.94 (.46–1.43)	3.82	<.001
	McRae et al. (2004) – Sertraline	.84 (.37–1.31)	3.52	<.001
	<i>Total</i>	0.42 (0.24–0.61)	4.43	<.001

Disorder	Study Name	Hedges' g (95% CI)	Z-Value	p-value
Social Anxiety Disorder	Bruce et al. (2012) – Paroxetine	.49 (.35–.63)	6.78	<.001
	Francois et al. (2008) – Citalopram	.11 (–.01–.32)	1.04	.297
	Liebowitz et al (2003) – Sertraline	.39 (.19–.59)	3.88	<.001
	Muehlbacher et al. (2005) – Mirtazapine	.93 (.41–1.45)	3.48	<.001
	<i>Total</i>	0.41 (.18–0.64)	3.51	<.001
All disorders		.41 (.31–.51)	7.84	<.001