Chapter 10

Initial severity and antidepressant efficacy for anxiety disorders: an individual patient data meta-analysis

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Submitted

Abstract

Objective: To examine the influence of initial severity on antidepressant efficacy for generalized anxiety disorder (GAD), social anxiety disorder (SAD), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and panic disorder (PD).

Methods: Individual patient data of 8,979 participants in 29 antidepressant trials were requested from Clinical Study Data Request. Mixed-effects models were used to investigate an interaction between initial severity and treatment group.

Results: For GAD, an interaction between treatment group and severity was found. The antidepressant-placebo difference was 1.4 (95% CI: 0.4-2.5, SMD: 0.15) points on the Hamilton Anxiety Rating Scale (HAM-A) for mildly ill participants (baseline HAM-A of 10), increasing to 4.0 (95% CI: 3.4-4.6, SMD: 0.43) or greater for severely ill participants (baseline HAM-A of 30).

For SAD, OCD, and PTSD, no interaction was found. Across severity levels, the mean difference was 16.1 (95% CI: 12.9-19.3, SMD: 0.59) on the Liebowitz Social Anxiety Scale (LSAS) for SAD, 3.4 (95% CI: 2.5-4.4, SMD: 0.39) on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) for OCD, and 10.3 (95% CI: 6.9-13.6, SMD: 0.41) on the Clinician-Administered PTSD Scale (CAPS) for PTSD.

For PD, the antidepressant-placebo difference in number of panic attacks/2 weeks was 0.4 (95% CI: 0.3-0.6) for participants with 10 panic attacks/2 weeks at baseline, increasing to 0.9 (95% CI: 0.7-1.2) for participants with 20, and to 4.7 (95% CI: 3.0-6.4) for participants with 40.

Conclusions: Antidepressants are equally effective across the severity range for SAD, OCD, and PTSD. For GAD and PD, however, antidepressant benefits are small at low severity.

Registration: NCT02476136

Introduction

Antidepressants are considered effective treatments for major depressive disorder (MDD) [11, 19] and anxiety disorders [12, 123, 187, 264]. However, research in MDD has suggested that antidepressant efficacy may depend upon initial symptom severity. Both trial-level [69, 70, 375] and individual patient data (IPD) meta-analyses [71, 72, 376] have found that antidepressants provide few benefits compared to placebo for patients with low initial severity. Consequently, many guidelines no longer recommend antidepressants for mild depression [74, 428].

A relationship between initial severity and efficacy has also been found for the use of antipsychotics in schizophrenia [430], which suggests that this is a cross-diagnostic phenomenon. Recently, however, two IPD meta-analyses, both substantially larger than previous analyses, did not find an association between initial severity and antidepressant efficacy for MDD [75, 76], indicating that this question is not yet settled.

Antidepressants are also commonly used for anxiety disorders [23], but comparatively little evidence is available for these disorders. Trial-level meta-analyses for OCD [78], generalized anxiety disorder (GAD) and panic disorder (PD) [77], and social anxiety disorder (SAD) [431, 432] found no evidence that antidepressant efficacy increases with increasing severity. We also found no support for an association between initial severity and treatment efficacy in a recent meta-analysis of 56 antidepressant trials for GAD, SAD, OCD, PTSD, and PD [433].

However, trial-level meta-regression analyses that examine a participant-level variable (such as initial severity) may be prone to the ecological fallacy [434], in which a trial-level relationship can be found that does not exist at the participant level, or vice versa. They can also be underpowered and suffer from a restriction of range, since using the mean baseline severity across participants will average out extreme scores. Hence, IPD is needed to provide better insight into whether initial severity is associated with antidepressant efficacy for anxiety disorders.

However, few studies have used IPD and most of these studies had significant limitations. Two studies examined efficacy in subgroups of less and more severely anxious patients (for GAD and SAD) without actually testing for differences between the subgroups [435, 436]. Two other patient-level analyses for GAD tested the association between severity and dichotomized outcomes, with one analysis reporting an association only between severity and remission [437] and the other only between severity and response [379]. Two patient-level analyses for SAD also found contradictory results, with one reporting greater efficacy in more severely anxious participants than in less severely anxious participants [378] while the other reported similar efficacy [438]. Finally, a post-hoc analysis of a trial for PTSD found no evidence for moderation by baseline severity, but this was a negative trial, which may have made it impossible to detect a moderation effect [439]. To our knowledge, there are no patient-level analyses for OCD or PD.

Given the limitations of the available evidence (including dichotomization of outcomes and predictors, which leads to a significant loss of power [440]) and the contradictory results, the question of whether initial severity moderates antidepressant efficacy for anxiety disorders, OCD, and PTSD remains unanswered. In the current study, we therefore examined this question using IPD from 29 trials enrolling 8,979 participants.

Methods

Data source

We requested IPD from Clinical Study Data Request, a multi-sponsor data-sharing platform [441]. We first identified all selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) developed by participating sponsors. These included paroxetine, fluoxetine, and duloxetine. We then identified all double-blind RCTs of these antidepressants for an anxiety disorder that were mentioned in Food and Drug Administration drug approval packages [20] or the GlaxoSmithKline [442] and Lilly [443] trial registries. We included only RCTs that were placebo-controlled, short-term ($\leq$ 16 weeks), and performed primarily in adults.

Primary outcomes

As our primary outcome, we chose the outcome usually considered primary for that disorder. For GAD, this was the Hamilton Rating Scale for Anxiety (HAM-A); for SAD, the Liebowitz Social Anxiety Scale (LSAS); for OCD, the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS); and for PTSD, the Clinician-Administered PTSD Scale (CAPS). For PD, most of the included trials used response as an outcome (defined as having 0 full panic attacks), but we selected the number of full panic attacks per 2 weeks, since dichotomizing a continuous outcome leads to a significant loss of information.

Patient population

We included patients with a valid baseline score on the primary outcome and at least one valid follow-up score. Patients assigned to placebo, the investigative antidepressant, or a comparator SSRI or SNRI were included. We excluded patients assigned to other active comparators (e.g. benzodiazepines).

Statistical analysis

We conducted separate analyses for each disorder. For GAD, SAD, OCD, and PTSD, we applied linear mixed models, using the nlme package (version 3.1-127) for R (version 3.3.0). The effect measure of interest was the change from baseline on the primary outcome. The initial model included all fixed effects, regardless of significance. These were initial severity, treatment group, linear and quadratic terms for time (in days since baseline), and their two- and three-way interactions. Baseline and change scores were grand-mean centered and standardized, while time was centered at trial endpoint and standardized.

Using this first model, we modeled the covariance structure of the nested data (observation within participant within trial). We considered a random intercept at the trial level and a random intercept plus random effects for linear and quadratic time at the participant level. For these random effects, we examined compound symmetry, diagonal, and unstructured covariance matrices. Additionally, we considered an autocorrelation term for the residuals. We used restricted maximum likelihood (REML) for estimation and the Akaike Information Criterion (AIC) to select the best-fitting covariance structure.

Subsequently, we refitted the model using maximum likelihood (ML) and removed the least significant fixed effects by backward selection. If an interaction or quadratic effect was significant, we retained all component main or linear effects regardless of significance. We used the AIC to select the best-fitting model. However, for clarity we further simplified models containing non-significant terms even if there was a marginal AIC difference in favor of the more complex model. In these cases, both the Bayesian Information Criterion (BIC) and (when applicable) the likelihood ratio test also favored the simpler models.

We calculated a standardized mean difference (SMD) by dividing the difference between the placebo and drug change scores by the pooled standard deviation of the change score at endpoint (imputed where necessary).

For PD, we applied a generalized linear (negative binomial) mixed model, using the glmer.nb command from the lme4 package (version 1.1-12). The effect measure of interest was the number of panic attacks per two weeks. Because this measure was highly skewed, we replaced values higher than 100 (45 (0.4%) of 11,785 observations) by a new value between 70 and 100 (randomly drawn from a uniform distribution) to improve the distribution and model convergence.

The initial model included the same fixed effects as for the other disorders. However, due to convergence problems, time was centered at the mean rather than at endpoint. For the covariance structure, we considered only a random trial-level intercept, and a random intercept and random effect for linear time at the participant level, as models including a random effect for quadratic time failed to converge. Since the lme4 package does not easily allow for either autocorrelation terms or various covariance structures, we

only modeled an unstructured covariance matrix.

We subsequently selected the best-fitting model using backward selection of the fixed effects, as done for the other disorders. Because of the non-normal distribution of panic attacks, we only calculated the endpoint scores and did not include a standardized difference for PD.

For all disorders, we also analyzed models that included age and gender as covariates. These yielded similar results as models without age and gender and are not described further.

Results

Trials and participants

We identified 34 trials, but we excluded one trial of paroxetine for PD [140] a priori, as it did not distinguish between full and limited-symptom panic attacks. We were denied access to 4 other trials: electronic data was not available for a trial of fluoxetine for OCD [166] (completed in 1991), while the translation costs for three Japanese trials of paroxetine for SAD [444, 445] and GAD [446] were considered prohibitive. One of these trials was positive, i.e. had statistically significant results for the primary outcome, while the other three were negative.

We received access to 29 trials with 3,656 placebo-treated and 5,323 antidepressant-treated participants. For GAD, we had access to 8 trials (6 positive) with 1,342 placebo-treated and 2,088 antidepressant-treated participants; for SAD, 4 trials (all positive) with 514 placebo-treated and 681 antidepressant-treated participants; for OCD, 4 trials (3 positive) with 350 placebo-treated and 782 antidepressant-treated participants; for PTSD, 3 trials (2 positive) with 459 placebo-treated and 612 antidepressant-treated participants; and for PD, 10 trials (5 positive) with 991 placebo-treated and 1,160 antidepressant-treated participants (see Table 10.1 for baseline characteristics and Table 10.4 in the Appendix for individual trial information).

GAD, SAD, OCD, and PTSD

For all four disorders, a model with an unstructured covariance matrix (including all random effects) and autocorrelated errors fit best. For GAD, the best-fitting model included the two-way interaction between baseline score and treatment group, but not the three-way interactions between baseline score, treatment group, and time (Figure 10.1a).

Table 10.1: *Baseline characteristics for each disorder*

	Female	Mean age	Baseline score		
Disorder	(%)	(SD)	Mean (SD)	Median (IQR)	Range
GAD	62.3	42.0 (13.4)	25.1 (5.9)		2 – 50
SAD	46.8	37.3 (11.0)	80.2 (24.0)		7 – 139
OCD	44.4	38.7 (12.4)	25.0 (5.3)		10 – 40
PTSD	62.6	41.1 (11.7)	75.2 (16.6)		30 – 132
PD	61.4	37.3 (10.5)		5 (3 – 11)	0 – 99

GAD: generalized anxiety disorder; OCD: obsessive-compulsive disorder; SAD: social anxiety disorder; PD: panic disorder; PTSD: post-traumatic stress disorder. The baseline score is based on the Hamilton Anxiety Rating Scale (HAM-A) for GAD, the Liebowitz Social Anxiety Scale (LSAS) for SAD, the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) for OCD, the Clinician-Administered PTSD Scale (CAPS) for PTSD, and the number of panic attacks/2 weeks for panic disorder.

For SAD, OCD and PTSD, the best-fitting model did not include any of the interactions between baseline score and treatment group (Figure 10.1b-d). Model specifications are available in Tables 10.5 and 10.6 in the Appendix.

For GAD, the estimated benefit of antidepressants (compared to placebo) at trial endpoint (8 weeks) was 1.4 (95% CI: 0.4-2.5, SMD: 0.15) points on the HAM-A for participants with a baseline score of 10, increasing to 4.0 (95% CI: 3.4-4.6, SMD: 0.43) for participants with a baseline score of 30 (see Table 10.2).

For SAD, OCD, and PTSD, the estimated benefit of antidepressants was the same across the severity range. For SAD, it was 16.1 (95% CI: 12.9-19.3, SMD: 0.59) points on the LSAS at week 12; for OCD, it was 3.4 (95% CI: 2.5-4.4, SMD: 0.39) points on the Y-BOCS at week 12; and for PTSD it was 10.3 (95% CI: 6.9-13.6, SMD: 0.41) points on the CAPS at week 12.

Panic disorder

For PD, the model with the lowest AIC (38267.2) contained the two-way interaction between baseline severity and group, but because this term was not significant ($p = 0.11$), we preferred a more parsimonious model without the interaction and with an only marginally larger AIC (38268.6 after removing two non-significant terms). Full specifications are provided in Tables 10.5 and 10.6 in the Appendix.

This parsimonious model indicated that the drug-placebo difference was constant on the log scale of the negative binomial model and hence that the *ratio* of the endpoint number of panic attacks/2 weeks in the placebo group compared to the drug group was constant (2.46) on the original scale. Consequently, the absolute difference between the drug and

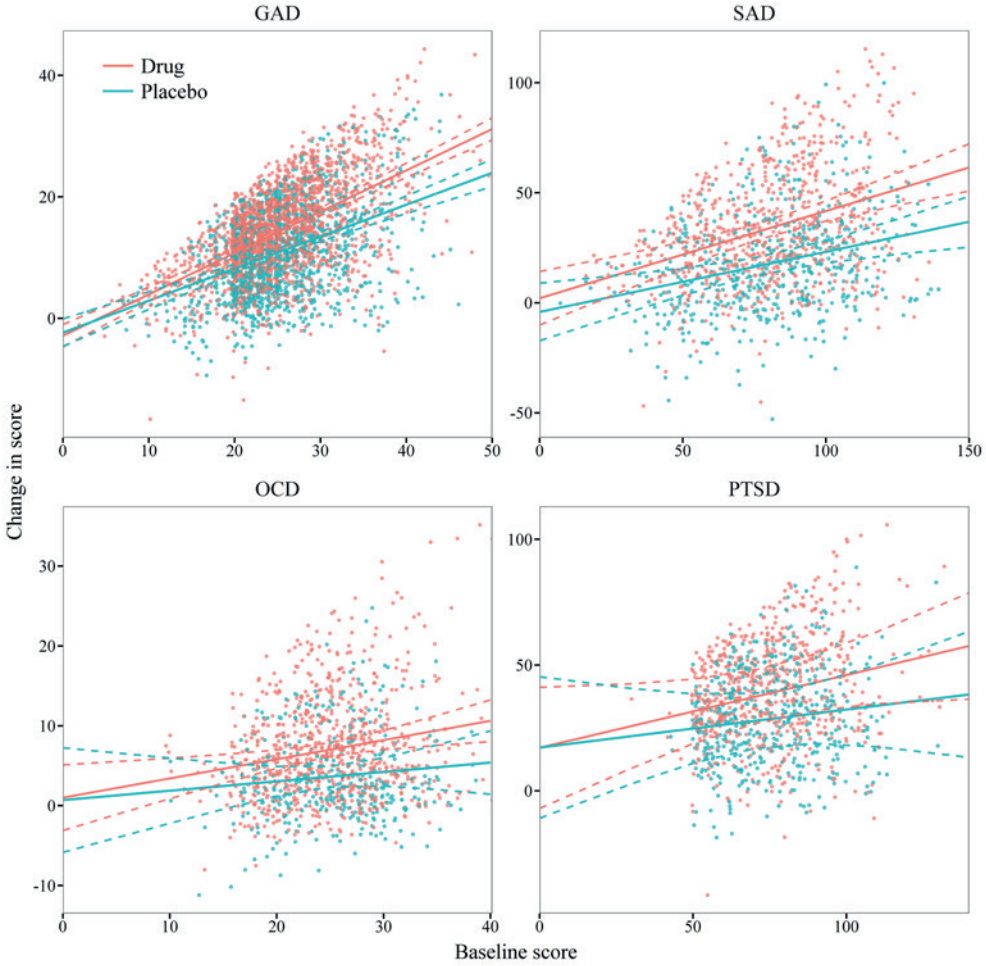

Figure 10.1: *Predicted change from baseline for antidepressant- and placebo-treated participants with generalized anxiety disorder (GAD), social anxiety disorder (SAD), obsessive-compulsive disorder (OCD), or post-traumatic stress disorder (PTSD). Predictions are derived from the full model, including non-significant interaction terms. Data points were jittered to reduce over-plotting.*

placebo groups actually increased with increasing severity (Figure 10.2).

For participants experiencing two panic attacks/2 weeks at baseline, the estimated drug-placebo difference was 0.2 (95% CI: 0.2-0.3) (in favor of antidepressants) at week 10. This increased to 0.4 (95% CI: 0.3-0.6) for participants experiencing 10 panic attacks/2 weeks at baseline, 0.9 (95% CI: 0.7-1.2) for participants experiencing 20 panic attacks/2 weeks at baseline, and 4.7 (95% CI: 3.0-6.4) for participants experiencing 40 panic attacks/2 weeks at baseline (Table 10.3).

Table 10.2: *Predicted change on the Hamilton Anxiety Rating Scale (HAM-A) and antidepressant-placebo difference after 8 weeks of treatment for GAD.*

		Predicted change (95% CI)			
Baseline	N	Placebo	Antidepressant	Diff. (95% CI)	SMD
10	79	2.7 (1.7 – 3.7)	4.1 (3.2 – 5.0)	1.4 (0.4 – 2.5)	0.15
15	259	5.4 (4.6 – 6.2)	7.4 (6.8 – 8.1)	2.1 (1.3 – 2.9)	0.22
20	1388	8.1 (7.5 – 8.7)	10.8 (10.3 – 11.3)	2.7 (2.1 – 3.3)	0.29
25	998	10.8 (10.3 – 11.3)	14.2 (13.7 – 14.6)	3.3 (2.8 – 3.9)	0.36
30	442	13.5 (12.9 – 14.1)	17.5 (17.0 – 18.0)	4.0 (3.4 – 4.6)	0.43
35	187	16.2 (15.5 – 17.0)	20.9 (20.2 – 21.5)	4.6 (3.8 – 5.4)	0.50
40	48	18.9 (17.9 – 20.0)	24.2 (23.3 – 25.1)	5.3 (4.2 – 6.3)	0.56
45	10	21.7 (20.4 – 22.9)	27.6 (26.5 – 28.7)	5.9 (4.6 – 7.2)	0.63

Baseline indicates the baseline score on the Hamilton Anxiety Rating Scale (HAM-A). N indicates the number of participants with a baseline score in between the indicated score and the subsequent score (e.g. 10 includes participants with baseline scores between 10 and 14) or the maximum score. Diff.: drug-placebo difference; GAD: generalized anxiety disorder; SMD: standardized mean difference.

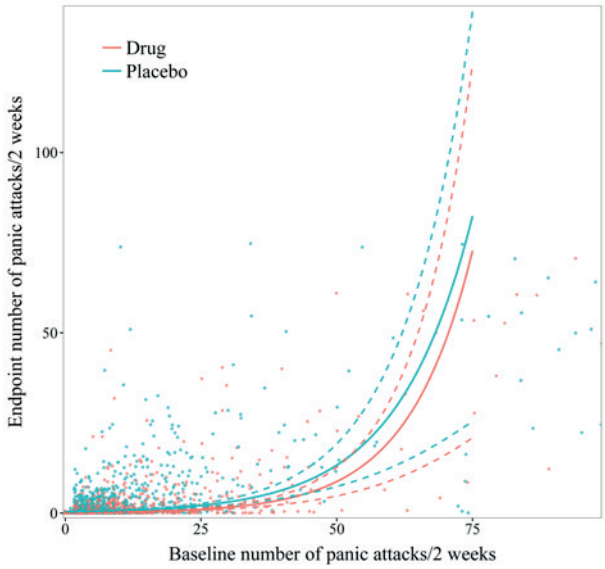

Figure 10.2: *Predicted number of panic attacks/2 weeks at endpoint for antidepressant- and placebo-treated participants with panic disorder. Predictions are derived from the full model, including non-significant interaction terms. Data points were jittered to reduce over-plotting.*

Table 10.3: *Predicted endpoint number of panic attacks/2 weeks and antidepressant-placebo difference after 10 weeks of treatment for panic disorder.*

		Predicted no. PAs/2 weeks (95% CI)		
Baseline	N	Placebo	Antidepressant	Diff. (95% CI)
2	636	0.38 (0.31 – 0.46)	0.15 (0.13 – 0.19)	0.23 (0.16 – 0.29)
4	396	0.44 (0.37 – 0.54)	0.18 (0.15 – 0.22)	0.26 (0.19 – 0.34)
6	258	0.52 (0.43 – 0.63)	0.21 (0.17 – 0.26)	0.31 (0.22 – 0.40)
8	175	0.61 (0.51 – 0.74)	0.25 (0.21 – 0.30)	0.36 (0.26 – 0.47)
10	240	0.72 (0.60 – 0.86)	0.29 (0.24 – 0.35)	0.43 (0.30 – 0.55)
15	123	1.07 (0.89 – 1.29)	0.43 (0.36 – 0.52)	0.64 (0.45 – 0.82)
20	133	1.59 (1.31 – 1.93)	0.65 (0.53 – 0.78)	0.95 (0.67 – 1.23)
30	58	3.54 (2.82 – 4.45)	1.44 (1.14 – 1.80)	2.10 (1.43 – 2.78)
40	44	7.86 (5.93 – 10.41)	3.19 (2.41 – 4.21)	4.67 (2.98 – 6.37)
60	37	38.76 (25.78 – 58.28)	15.72 (10.50 – 23.55)	23.04 (12.23 – 33.83)

Baseline indicates the baseline number of panic attacks (PAs)/2 weeks. N indicates the number of participants with a baseline score in between the indicated score and the subsequent score (e.g. 2 includes participants with baseline scores of 2 or 3) or the maximum score (99). Diff.: drug-placebo difference.

Discussion

Principal findings

This is the first individual patient data meta-analysis examining the relationship between baseline severity and antidepressant efficacy for anxiety disorders. We showed that initial severity moderates antidepressant efficacy for GAD, but not for SAD, OCD, and PTSD. For PD, the ratio between the number of panic attacks in the placebo group compared to the drug group was constant, but the absolute difference between antidepressants and placebo was small for patients experiencing few panic attacks at baseline and increased with increasing severity. For all disorders, a regression to the mean effect occurred, but this cannot explain the interaction between baseline severity and treatment in GAD.

Our findings are in agreement with our earlier trial-level meta-analysis for SAD, OCD, and PTSD, but not for GAD and PD [433]. These differences are likely because of the much larger sample size and the use of IPD in this study. The SMDs for SAD and PTSD were also larger than those found earlier [20], which is probably due in part to trial selection, as the paroxetine trials had higher effect sizes than trials of other drugs for these disorders, and in part to different analytical techniques.

Because the non-normal primary outcome necessitated an alternative analytical approach, our findings for PD are difficult to compare to the other disorders. However, it is interesting that we found a relationship between initial severity and antidepressant efficacy for GAD, but not for SAD, OCD, and PTSD.

GAD is often considered to be more closely related to MDD than the other anxiety disorders. In factor analyses, GAD often clusters with depression in a 'distress' dimension while other anxiety disorders cluster in a 'fear' dimension [5], although PTSD may also load primarily on the 'distress' dimension [447, 448]. Additionally, the HAM-A overlaps with the Hamilton Depression Rating Scale (HAM-D) commonly used in MDD trials.

On the other hand, since the association between initial severity and antidepressant efficacy in MDD has been called into question [75, 76], a greater similarity between MDD and GAD might not explain our findings. HAM-A items also tend to be relatively non-specific, covering such common symptoms as insomnia, tension, worries, and pains, while the LSAS and Y-BOCS questionnaires specifically examine the distress associated with respectively feared social situations and obsessions or compulsions, and the CAPS questionnaire examines both general distress symptoms and specific trauma-related distress. Such general distress symptoms, particularly when mild, may be more responsive to placebo or more likely to improve spontaneously, which could explain why antidepressants provide little benefit over placebo in mild GAD.

However, it is also important to note that we had the largest sample size for GAD. Although we had more than 1000 participants for each disorder and hence should have been able to detect a substantial interaction effect if it existed, it is possible that smaller interaction effects for the other disorders were missed. However, these are less likely to be of clinical significance.

Strengths and limitations

The main strength of this study is that we used IPD and had a large sample size for each disorder. Furthermore, we used disorder-specific primary outcomes and made full use of the longitudinal data by employing mixed models.

Our study is limited by the limitations of the included trials. In particular, minimum severity criteria restricted the number of participants at the low end of the severity range for some disorders. Half of the GAD trials specified a minimum HAM-A score of 20, for instance, even though most primary care patients diagnosed with GAD have scores lower than 20 [449]. Hence, our findings are most clearly applicable to patients who are moderately or severely ill and less so to patients with subthreshold or very mild symptoms. The included trials also frequently excluded patients with comorbid disorders such as MDD, even though these disorders commonly occur together [4].

Furthermore, our findings for PD are difficult to compare to the other disorders. The best-fitting model showed that the ratio of the number of panic attacks at endpoint in the placebo group compared to the drug group remained constant, but this means that the drug-placebo difference increased with increasing severity. We have emphasized the latter, because this measure is most comparable to the other disorders, but other choices could

be made. Additionally, while the number of panic attacks is a clinically relevant outcome, other important facets of PD, such as agoraphobia, were not examined. Our results may have been different if we had been able to use a more comprehensive questionnaire, such as the Panic Disorder Severity Scale [450].

We also did not receive data for four trials. Since three of these trials were negative, we may have overestimated the antidepressant effect for GAD, SAD, and OCD, but it seems unlikely that this would have affected our findings regarding initial severity. Negative trials will probably show little evidence for differential efficacy, so it is not likely that we would have found a significant interaction effect for SAD and OCD if we had been able to include participants from these trials. For GAD, the evidence in favor of an interaction effect was sufficiently strong that it probably would have remained even if we had added an additional trial in which differential efficacy was not apparent.

Finally, we included only trials of duloxetine, paroxetine, and fluoxetine. We used Clinical Study Data Request because it allowed us to obtain a nearly complete set of trials for these drugs. Other approaches (e.g., a comprehensive literature search followed by requesting IPD from authors) would almost certainly have introduced much more significant biases into our trial selection, because of reporting bias [20] and refusal or inability to share data. For example, a study that took this approach for MDD trials only received data for 6 of 23 eligible trials [72]. However, future research should examine other antidepressants.

Clinical implications

To understand the implications of these findings, it should be noted that the clinical relevance of a treatment effect is context-specific, depending on such factors as the expected sequelae of the disease, the costs and drawbacks of the treatment, and the efficacy of alternative treatments [451]. Without an agreed-upon cut-off point for a clinically relevant effect, it is difficult to establish a threshold below which the effects of antidepressants for GAD and PD are not clinically meaningful. For GAD, the SMDs do suggest that the antidepressant-placebo difference is small for patients with a baseline severity score of 15 or less.

Even without a definite cut-off point, though, it is clear that the risk-benefit ratio for GAD and PD becomes less favorable as initial severity decreases. It is therefore imperative that clinicians transparently discuss the expected benefits of antidepressants with patients with mild to moderate symptoms, who constitute the majority of treatment-seeking patients in primary care [449]. To our knowledge, there is no evidence that alternative treatments, such as psychotherapy, would be more effective than antidepressants for patients with mild GAD or PD. These modalities may nevertheless be preferable as they are often thought to have fewer adverse effects (although poor monitoring limits our understanding of the negative effects of psychotherapy [47, 49]).

There was no evidence for a relationship between initial severity and antidepressant efficacy for SAD, OCD, and PTSD. Nevertheless, other factors, such as anticipated course, patient preferences, and the availability, acceptability, and efficacy of alternative treatments, could still lead to different prescribing decisions for mild versus severe disorders, even in the absence of differential efficacy.

Conclusions

We found that antidepressants are equally effective across the severity range for SAD, OCD, and PTSD. For GAD and PD, however, the benefits of antidepressants over and above placebo are small to negligible at low severity. The trade-off between benefits and risks may therefore be unfavorable for these patients, and alternative approaches that might have fewer risks, such as guided self-help or cognitive-behavioral therapy, may be preferred as first-line treatment.

Appendix

Table 10.4: *Supplemental table of studies*

Disorder	Drug	Trial	Dose (mg/day)	Duration (weeks)	Sample size		Baseline
					Drug	Placebo	Mean (SD)
GAD	Duloxetine	HMBR [134]	60, 120	9	334	173	25.3 (7.4)
		HMDT [135]	60 – 120	10	161	158	23.0 (7.7)
		HMDW [452]	60 – 120 V 75 – 225	10	392	163	27.5 (7.5)
		HMDU [136]	60 – 120 V 75 – 225	10	308	158	25.2 (5.7)
	Paroxetine	637 [126]	20 – 50	8	184	184	25.6 (4.5)
		641 [132]	20, 40	8	385	180	24.1 (3.6)
		642 [133]	20 – 50	8	161	163	24.1 (3.6)
	Paroxetine CR	791 [453]	12.5 – 37.5	8	163	163	24.6 (3.7)
SAD	Paroxetine	382 [152]	20 – 50	12	90	92	80.3 (23.5)
		454 [153]	20, 40, 60	12	275	93	77.3 (23.0)
		502 [151]	20 – 50	12	131	145	86.4 (24.5)
	Paroxetine CR	790 [154]	12.5 – 37.5	12	185	184	78.5 (24.0)
OCD	Fluoxetine	HCEP [165]	20, 40, 60	13	259	88	24.1 (5.4)
	Paroxetine	116 [169]	20, 40, 60	12	250	88	25.4 (5.2)
		118 [454]	20 – 60	12	79	75	24.2 (4.8)
		136 [170]	20 – 60	12	194	99	25.9 (5.2)
PTSD	Paroxetine	627 [127]	20 – 50	12	154	159	77.9 (17.9)
		648 [164]	20 – 50	12	136	133	73.4 (16.1)
		651 [163]	20, 40	12	322	167	74.5 (15.8)
Panic disorder	Fluoxetine	HCJC [429]	20 – 60	12	90	90	7.8 (6.6)
		HCJB (N/A)	20 – 60	12	106	104	6.8 (7.1)
		HCHG (N/A)	10, 20	10	145	63	10.7 (16.4)
		HCHQ (N/A)	20	8	56	65	22.4 (41.9)
	Paroxetine	120 [139]	10, 20, 40	10	182	66	10.2 (15.9)
		187 [141]	20 – 60	12	109	113	12.5 (13.8)
		223 [455]	10 – 60	10	68	67	8.4 (9.2)
	Paroxetine CR	494 [142]	25 – 75	10	127	137	10.4 (20.9)
		495 [142]	25 – 75	10	143	155	10.0 (12.7)
		497 [142]	25 – 75	10	134	131	8.8 (11.8)

N/A indicates unpublished trials for which a registry summary could not be located. These trials were identified in the Food and Drug Administration drug application package for fluoxetine for panic disorder. CR: controlled release; GAD: generalized anxiety disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SAD: social anxiety disorder; V: venlafaxine (used as an active comparator).

Table 10.5: *Model comparisons*

Disorder	Model	Specifications	DF	AIC	BIC	Log-likelihood or deviance (PD only)
GAD	1	Full model	21	32046.47	32209.12	-16002.23
	2	Model 1 - $B \times G \times T^2$	20	32044.61	32199.52	-16002.31
	3	Model 2 - $B \times G \times T$	19	32043.03	32190.19	-16002.51
	4	Model 3 - $B \times G$	18	32058.99	32198.41	-16011.49
SAD	1	Full model	21	10633.50	10778.63	-5295.749
	2	Model 1 - $B \times G \times T^2$	20	10632.75	10770.96	-5296.372
	3	Model 2 - $B \times G \times T$	19	10631.48	10762.79	-5296.741
	4	Model 3 - $B \times G$	18	10631.06	10755.45	-5297.528
	5	Model 4 - $B \times T^2$	17	10637.17	10754.65	-5301.583
OCD	1	Full model	21	13500.48	13646.47	-6729.238
	2	Model 1 - $B \times G \times T^2$	20	13498.79	13637.84	-6729.396
	3	Model 2 - $B \times G \times T$	19	13498.10	13630.19	-6730.050
	4	Model 3 - $B \times G$	18	13496.15	13621.29	-6730.076
	5	Model 4 - $B \times T^2$	17	13498.81	13617.00	-6732.405
PTSD	1	Full model	21	7152.29	7281.26	-3555.145
	2	Model 1 - $B \times G \times T^2$	20	7150.42	7273.24	-3555.210
	3	Model 2 - $G \times T^2$	19	7149.29	7265.97	-3555.643
	4	Model 3 - $B \times G \times T$	18	7148.57	7259.12	-3556.285
	5	Model 4 - $B \times G$	17	7146.98	7251.38	-3556.489
	6	Model 5 - $B \times T^2$	16	7146.47	7244.74	-3557.235
	7	Model 6 – $B \times T$	15	7149.19	7241.32	-3559.597
PD	1	Full model	17	38269.0	38390.9	38235.0
	2	Model 1 - $B \times G \times T^2$	16	38269.1	38383.9	38237.1
	3	Model 2 - $G \times T^2$	15	38267.8	38375.4	38237.8
	4	Model 3 - $B \times G \times T$	14	38267.2	38367.6	38239.2
	5	Model 4 - $B \times G$	13	38267.8	38361.0	38241.8
	6	Model 5 - $B \times T^2$	12	38268.6	38354.6	38244.6
	7	Model 6 - T^2	11	38274.7	38353.6	38252.7

B: baseline score; G: group (drug vs. placebo); T: time (in days since baseline); T^2: quadratic time. AIC: Akaike information criterion; BIC: Bayes information criterion; DF: degrees of freedom; GAD: generalized anxiety disorder; OCD: obsessive-compulsive disorder; PD: panic disorder; PTSD: post-traumatic stress disorder; SAD: social anxiety disorder.

Table 10.6: *Model specifications*

		Full model			Best-fitting model		
Disorder	Parameter	β	SE	p-value	β	SE	p-value
GAD	Intercept	0.189	0.033	<0.001	0.189	0.033	<0.001
	T	0.015	0.018	0.390	0.015	0.018	0.390
	T^2	-0.127	0.008	<0.001	-0.127	0.008	<0.001
	G	0.420	0.035	<0.001	0.420	0.035	<0.001
	B	0.391	0.027	<0.001	0.403	0.022	<0.001
	$T \times G$	0.019	0.023	<0.001	0.019	0.023	0.405
	$T^2 \times G$	-0.049	0.010	<0.001	-0.049	0.010	<0.001
	$T \times B$	0.0383	0.016	0.019	0.039	0.010	<0.001
	$T^2 \times B$	-0.023	0.007	0.002	-0.025	0.004	<0.001
	$B \times G$	0.115	0.035	<0.001	0.095	0.022	<0.001
	$B \times G \times T$	0.002	0.021	0.941	-	-	-
	$B \times G \times T^2$	-0.004	0.009	0.706	-	-	-
SAD	Intercept	0.164	0.055	0.003	0.163	0.055	0.003
	T	-0.012	0.028	0.665	-0.012	0.028	0.672
	T^2	-0.074	0.010	<0.001	-0.074	0.010	<0.001
	G	0.710	0.071	<0.001	0.711	0.071	<0.001
	B	0.289	0.052	<0.001	0.359	0.035	<0.001
	$T \times G$	0.134	0.037	<0.001	0.134	0.037	<0.001
	$T^2 \times G$	-0.033	0.013	0.008	-0.034	0.013	0.008
	$T \times B$	0.049	0.028	0.076	0.059	0.019	0.001
	$T^2 \times B$	-0.014	0.009	0.120	-0.016	0.006	0.010
	$B \times G$	0.130	0.070	0.065	-	-	-
	$B \times G \times T$	0.018	0.037	0.624	-	-	-
	$B \times G \times T^2$	-0.004	0.013	0.770	-	-	-
OCD	Intercept	-0.058	0.067	0.380	-0.063	0.067	0.346
	T	-0.045	0.044	0.304	-0.045	0.044	0.305
	T^2	-0.066	0.015	<0.001	-0.066	0.015	<0.001
	G	0.559	0.080	<0.001	0.562	0.080	<0.001
	B	0.102	0.069	0.142	0.178	0.037	<0.001
	$T \times G$	0.072	0.052	0.163	0.072	0.052	0.166
	$T^2 \times G$	-0.046	0.018	0.011	-0.047	0.018	0.010
	$T \times B$	-0.010	0.046	0.833	-0.006	0.024	0.813
	$T^2 \times B$	-0.010	0.016	0.520	-0.018	0.008	0.034
	$B \times G$	0.107	0.082	0.195	-	-	-
	$B \times G \times T$	0.005	0.054	0.928	-	-	-
	$B \times G \times T^2$	-0.011	0.019	0.552	-	-	-
PTSD	Intercept	0.127	0.104	0.220	0.129	0.104	0.216
	T	0.055	0.047	0.241	0.025	0.035	0.481
	T^2	-0.072	0.017	<0.001	-0.084	0.012	<0.001
	G	0.423	0.071	<0.001	0.425	0.071	<0.001
	B	0.103	0.056	0.062	0.159	0.035	<0.001
	$T \times G$	0.016	0.062	0.796	0.068	0.025	0.006

continued

Table 10.6: *Model specifications*

		Full model			Best-fitting model		
Disorder	Parameter	β	SE	p-value	β	SE	p-value
	$T^2 \times G$	-0.020	0.022	0.355	-	-	-
	$T \times B$	-0.011	0.047	0.816	-0.026	0.012	0.034
	$T^2 \times B$	-0.008	0.016	0.610	-	-	-
	$B \times G$	0.095	0.072	0.185	-	-	-
	$B \times G \times T$	0.006	0.061	0.923	-	-	-
	$B \times G \times T^2$	-0.008	0.021	0.721	-	-	-
Panic disorder	Intercept	0.446	0.070	<0.001	0.435	0.069	<0.001
	T	-0.671	0.030	<0.001	-0.673	0.068	<0.001
	T^2	0.027	0.030	0.084	0.033	0.011	0.004
	G	-0.493	0.071	<0.001	-0.464	0.068	<0.001
	B	0.846	0.045	<0.001	0.903	0.032	<0.001
	$T \times G$	-0.357	0.040	<0.001	-0.362	0.039	<0.001
	$T^2 \times G$	0.027	0.023	0.241	-	-	-
	$T \times B$	0.092	0.024	<0.001	0.114	0.018	<0.001
	$T^2 \times B$	-0.004	0.011	0.722	-	-	-
	$B \times G$	0.144	0.065	0.026	-	-	-
	$B \times G \times T$	0.037	0.035	0.295	-	-	-
	$B \times G \times T^2$	-0.024	0.017	0.148	-	-	-

B: baseline score; G: group (drug vs. placebo); T: time (in days since baseline); T^2: quadratic time. GAD: generalized anxiety disorder; OCD: obsessive-compulsive disorder; PD: panic disorder; PTSD: post-traumatic stress disorder; SAD: social anxiety disorder.