ORIGINAL ARTICLE

The efficacy of antidepressants for generalized anxiety disorder: a systematic review and meta-analysis

A eficácia dos antidepressivos para transtorno de ansiedade generalizada: uma revisão sistemática e metanálise

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Abstract

Objective: *To investigate the efficacy and acceptability of antidepressants in the treatment of generalized anxiety disorder.* ***Methods:*** *All randomized controlled trials assessing the use of antidepressants in generalized anxiety disorder up to may 2002 were included. Non randomized trials and those that included patients with both generalized anxiety disorder and another Axis I co-morbidity were excluded. Relative risks, weighted mean difference and number needed to treat were estimated. People who died or dropped out were regarded as having had no improvement.* ***Results:*** *Antidepressants (imipramine, venlafaxine and paroxetine) were found to be superior to placebo in treating generalized anxiety disorder. The calculated number needed to treat for antidepressants in generalized anxiety disorder was 5.15. Dropout rates did not differ between antidepressants and placebo.* ***Conclusion:*** *The available evidence suggests that antidepressants would probably be a reasonable treatment for generalized anxiety disorder patients in the clinical context.*

Keywords: Anxiety disorders/drug therapy; Antidepressive agents/therapeutic use; Randomized controlled trials; Review, academic [Publication type]; Meta-analysis

Resumo

Objetivos: *Investigar a eficácia e tolerabilidade dos antidepressivos no tratamento do Transtorno de ansiedade generalizada (TAG).* ***Métodos:*** *Todos os ensaios clínicos randomizados que investigavam o uso de antidepressivos para Transtorno de ansiedade generalizada até maio de 2002 foram incluídos nesta revisão. Ensaios clínicos não randomizados e aqueles que incluíram pacientes com Transtorno de ansiedade generalizada e outra comorbidade de Eixo I foram excluídos. Riscos relativos, diferenças de médias e número necessário para tratar (NNT) foram estimados. Pessoas que morreram ou saíram dos estudos foram considerados como sem melhora.* ***Resultados:*** *Antidepressivos (imipramina, venlafaxina e paroxetina) foram superiores ao placebo no tratamento do Transtorno de ansiedade generalizada. O número necessário para tratar para os antidepressivos em Transtorno de ansiedade generalizada foi 5,15. Taxas de abandono não diferiram entre antidepressivos e placebo.* ***Conclusão:*** *A evidência disponível sugere que os antidepressivos são um tratamento adequado para pacientes com Transtorno de ansiedade generalizada.*

Descritores: *Transtornos da ansiedade/quimioterapia; Agentes antidepressivos/uso terapêutico; Ensaios controlados aleatórios; Revisão acadêmica [Tipo de publicação]; Metanálise*

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Introduction

Generalized anxiety disorder (GAD) is characterized by excessive, pervasive and uncontrollable worry. Associated symptoms include irritability, restlessness and concentration problems. Somatic symptoms of GAD include muscle tension, sweating, dry mouth, nausea and diarrhea.[1] GAD is a chronic and recurrent disorder with a low rate of remission.[2] GAD has a considerable impact on quality of life and is associated with increased reliance in public assistance, impaired social life and low ratings of life satisfaction.[3] The current and lifetime prevalence of GAD have been estimated to be 1.6% and 5.1% respectively.[4] The lifetime prevalence of psychiatric comorbidities in GAD patients can reach over 90%.[4] The most common co-morbidities are major depressive disorder (62%) and dysthymia (39%).[5] Comorbidities such as major depression do not appear to change the course of GAD.[6]

Benzodiazepines and non benzodiazepine anxiolytics such as buspirone have been the mainstay for the treatment of GAD in the past.[7] As GAD tends to be a chronic condition, long-term pharmacological treatment is often necessary. This raises concern about the use of benzodiazepines, since these compounds may be associated with risks of abuse and dependence. Buspirone is devoid of the dependence risks associated with benzodiazepines, however it has a more limited spectrum of efficacy and delayed onset of action when compared to other treatments.

A variety of psychotherapeutic approaches have been used to treat GAD. To date, the most consistent results on the psychotherapy of GAD comes from the cognitive-behavioral therapy (CBT) approach. Results from well-conducted trials suggest that CBT can produce clinically relevant and long term therapeutic improvements as compared with controls. Psychotherapeutic approaches also seem to be well tolerated by patients and the dropout rates in clinical trials are low.[8] There are also data supporting the notion that psychotherapy may have an additional impact in the comorbid conditions associated to GAD.[8]

The first trial assessing the effect of antidepressants in GAD, diagnosed according to DSM-III criteria, was conducted by Hoehn-Saric et al.[9] These authors compared alprazolam and imipramine in a group of 52 GAD patients. They showed that both drugs were effective in treating GAD. However, imipramine was more effective in attenuating psychological symptoms such as dysphoria and anticipatory negative thinking, whereas alprazolam was more effective in somatic symptoms and in the hyperarousal associated with GAD. The same trend was detected by Rickels et al[10] in a comparison between imipramine, trazodone, diazepam and placebo. Rickels et al[10] showed that from week 3 through week 8, trazodone achieved similar anxiolytic efficacy to diazepam; the effect of imipramine was found to be somewhat better, and psychological symptoms such as apprehension and worry responded better to the antidepressants than to anxiolytics. A study by Rocca and associates,[11] within a sample of DSM-IV diagnosed GAD patients, supported the theory that antidepressants affect predominantly psychological symptoms whereas benzodiazepine affect predominantly somatic symptoms in GAD. A comparison between antidepressants and non benzodiazepine anxiolytics is available only for venlafaxine and buspirone.[12] This study included 365 patients and showed that venlafaxine and buspirone were superior to placebo in the majority of outcomes considered. There is also evidence that the management of benzodiazepine discontinuation in GAD patients can be facilitated by co-prescribing imipramine but not buspirone.[13]

In the light of the data presented, there are reasons to believe that antidepressants may offer a valuable alternative in the treatment of GAD patients. In the present review, randomized controlled trials (RCT) data on the use of antidepressants for treating GAD were assessed.

Aims of the study: To assess the efficacy and acceptability of antidepressants for treating generalized anxiety disorder.

Methods

1. Types of studies

All relevant randomized controlled trials comparing antidepressants to placebo or to another active pharmacological treatment (*see* Selection of trials).

2. Types of participants

People with a diagnosis of generalized anxiety disorder irrespective of gender, race, age or nationality.

Exclusion criteria: patients with generalized anxiety disorder and another Axis I co-morbidity.

3. Types of interventions

1) Any type of antidepressant.

2) Control treatments (any active drug or placebo). Whenever a placebo arm was present in the study, the comparison included in the metanalysis was antidepressant *vs* placebo.

4. Types of outcome measures

Primary outcomes of interest were:

1) Generalized anxiety changes at the end of trial

a) absence of treatment response as defined in the studies (treatment response is defined as absence of sufficient symptoms to meet diagnostic criteria for generalized anxiety disorder; scores of 1 or 2 in the Clinical Global impression Scale, which is a continuous scale of 7 grades, where 1 = very much improved, 2 = much improved... and 7 = very much worse);

2) Acceptability of the treatment as measured by:

a) the number of people dropping out during the trial, and post randomization exclusions;

b) specific side-effects.

5. Search strategy for identification of studies

1) Electronic databases:

The following electronic databases were searched:

a) The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR) up to May 2002;

b) The Cochrane Central Register of Controlled Trials (CENTRAL) (previously CCTR);

c) MEDLINE (1966-May 2002)

d) LILACS (1982-May 2002)

The MEDLINE and LILACS (up to May 2002) searches also acted as a quality assessment whereby the comprehensiveness and completeness of the two Cochrane registers were evaluated.

The terms used in the search were: anxiety or anxiety disorder and pharmacotherapy-5ht or pharmacotherapy-ad or pharmacotherapy-maoi or pharmacotherapy-nari or pharmacotherapy-rima or pharmacotherapy-r-ssri or pharmacotherapy-r-tca or pharmacotherapy-snri or pharmacotherapy-ssri or pharmacotherapy-tca.

2) Conference abstracts were searched.

3) Personal communication: in order to ensure that as many RCTs as possible would be identified, the authors of included

studies were consulted to find out if they know of any published or unpublished RCTs/ CCTs on pharmacological treatment of GAD which had not yet been identified. A list of all RCTs identified from other sources was sent to the authors.

4) Attempts were made to obtain unpublished trials from pharmaceuticalcompanies.

5) Book chapters on treatment of GAD were reviewed.

6. Selection of trials

One reviewer screened the abstracts of all publications that were obtained by the search strategy. A distinction was made between:

1) Eligible studies, in which antidepressants were compared to placebo or another drug;

2) Studies without any control element; studies of general treatment for GAD rather than pharmacological; studies of drug treatments other than antidepressants.

For abstracts where the authors found any indication of a clinical trial, the full article was obtained and inspected to assess its relevance to this review.

7. Quality assessment

In order to ensure that variation was not caused by systematic errors in the design of a study, the methodological quality of the selected trials was assessed by two independent reviewers. The methodological quality was assessed using the criteria described in the Cochrane Handbook . It is based on the evidence of a strong relationship between the potential for bias in the results and the allocation concealment and is defined as below:

1) Low risk of bias (adequate allocation concealment).

2) Moderate risk of bias (unclear method of allocation concealment).

3) High risk of bias (inadequate allocation concealment).

For the purpose of the analysis in this review, trials were included if they met criteria A or B as described in the Cochrane Handbook.

8. Data management

Data were independently extracted by two reviewers. Any disagreement was discussed with a third reviewer, decisions were documented and, where necessary, the study authors contacted to resolve the issue. All exclusions/dropouts were identified. If no information was available (either from the report or the authors) it was assumed that dropouts were due to side effects/treatment failure.

9. Analysis

In the statistical analysis, the relative risk (RR) and 95% confidence interval for dichotomous variables were calculated using the random effects model, as it takes into account of any between study differences (even if there is no statistically significant heterogeneity) and gives the same result as the fixed effects model when there is no between-study variance. Review Manager Software 4.1 was used to analyse the results. In the efficacy analysis, the number needed to treat (NNT) was also calculated, using 95% confidence intervals. The NNT is defined as the inverse of differences of risk between groups. The NNT expresses the number of patients that have to be treated in order to achieve one additional response, when compared to the control group.

Results

1. Included studies

The main features of the included studies are displayed in Table 1. Eight studies were considered most of them comparing Venlafaxine with placebo.

2. Efficacy analysis

All antidepressants vs placebo:

The efficacy analysis included the following studies from wich data could be extracted: Rickels 1993,[10] Davidson 1999,[12] Gelenberg 2000[14] and Pollack 2001.[15] Other included studies were used in the analysis of number of dropouts and specific side effects.

In general, short-term treatment response was more likely in patients receiving antidepressants than placebo. One study,[10] compared four treatments (imipramine, trazodone, diazepam and placebo). As imipramine was considered a reference antidepressant, we used the 'imipramine *vs* placebo' comparison rather than 'trazodone *vs* placebo'. Considering all trials, the pooled RR for non treatment response was 0.70 (95% confidence interval (CI) 0.62 to 0.79), favouring antidepressant treatment. The calculated NNT was 5.5 (95% CI 4.1 to 8.4).

- Imipramine:[10] The calculated RR was 0.67 (95% CI 0.50 to 0.91) and the NNT was 4.0 (95% CI 2.4 to 13.7).

- Venlafaxine:[12,14] The calculated RR for non treatment response was 0.68 (95% CI 0.46 to 0.99), and the calculated NNT was 5.0 (95% CI 3.58 to 8.62) . The studies carried out by Rickels 2000[13] and Allgulander 2001[16] could not be used for the efficacy analysis, as data could not be extracted as reported.

- Paroxetine:[15] The calculated RR was 0.72 (95% CI 0.56 to 0.92), and the calculated NNT was 6.72 (95% CI 3.9 to 24.7).

- Paroxetine vs imipramine:[17] The calculated RR was 1.73 (95% CI 0.31 to 9.57).

Sertraline vs placebo in children and adolescents:

- Sertraline:[18] This study was not included in the meta analysis because it studied children and adolescents. The results obtained in this small trial (N = 22) were very compelling, showing a calculated NNT of 1.22 (95% CI 0.90 to -1.7).

3. Acceptability

1) Dropouts (Table 3)

No significant differences were found between antidepressants and placebo. The RR for dropout for any antidepressant was 0.95 (95% CI 0.84 to 1.09). Similarly, when individual antidepressants were considered, no differences were found between individual treatments and the placebo group:

- Imipramine: RR = 0.71 (95% CI 0.41 to 1.24);
- Venlafaxine: RR = 0.86 (95% CI 0.72 to 1.02);
- Sertraline: RR = 0.45 (95% CI 0.03 to 5.84);
- Paroxetine: RR = 1.15 (95% CI 0.74 to 1.78); and
- Paroxetine vs imipramine: RR = 1.62 (95% CI 0.58 to 4.48).

2) Common drug specific side effects:

Overall, side effects were more common in the drug treated than in the placebo treated groups. Data for more than one trial were available only for venlafaxine:

- Venlafaxine:[12,14] those taking venlafaxine were more likely to report nausea, dry mouth, insomnia, constipation, somnolence, anorexia, sexual dysfunction and flatulence.

Table 1 – Characteristics of included studies

Study ID	Methods	Participants	Interventions	Outcomes
Allgulander 2001	1. Randomized	1. Diagnosis: GAD (DSM-IV)	1. Placebo (N = 130)	1. Dropouts rates
	2. Double blind	2. N = 541	2. Venlafaxine 37.5 mg/d (N = 140)	2. CGI scores
	3. Four parallel groups (placebo, venlafaxine 37.5, 75 and 150 mg/d)	3. Age (mean and SD): placebo + 46.1 (range 18-86); venlafaxine 37.5 mg/d = 45.4 (range 19-79); venlafaxine 150 mg/d = 45 (range 20-82)	3. Venlafaxine 75 mg/d (N = 134)	3. HAM-A scores
	4. Duration: 24 weeks	4. Sex: placebo = 58% females; venlafaxine 37.5 mg/d = 57% females; venlafaxine 75 mg/d = 62% females; venlafaxine 150 mg/d = 65% females	4. Venlafaxine 150 mg/d (N = 137)	4. Hospital anxiety and depression scale
	5. Analysis: LOCF	5. Setting: outpatients		5. The brief scale for anxiety
		6. History: excluded psychiatric disorder other than GAD		6. Self-rated social adjustment scale
				7. Physician Withdrawal Checklist
Davidson 1999	1. Randomized	1. Diagnosis: GAD (DSM-IV)	1. Placebo (N = 98)	1. Dropout rates
	2. Double blind	2. N = 405	2. Venlafaxine 75 mg/d (N = 87)	2. CGI scores
	3. Four parallel groups (placebo, venlafaxine 75 mg/d, venlafaxine 150 mg/d, buspirone 30 mg/d)	3. Age (mean and SD) placebo = 39 (11); venlafaxine 75 mg/d = 38 (10); venlafaxine 150 mg/d = 37 (11); buspirone 30 mg/d = 37 (10) Sex: 61.4% females Setting: outpatients History: excluded any significant psychiatrc disorder other than GAD	3. Venlafaxie 150 mg/d (N = 97)	3. HAM-A endpoint scores
	4. Duration: 8 weeks			4. Patient-rated hospital anxiety and depression scale
	5. Analysis: LOCF			5. Covi Anxiety Scale
				6. Raskin Depression Scale
Gelenberg 2000	1. Randomized	1. Diagnosis: Gad (DSM-IV)	1. Placebo (N = 127)	1. Dropout rates
	2. Double blind	2. N = 251	2. Venlafaxine 75-150 mg/d (N = 124)	2. CGI scores
	3. Two parallel groups	3. Age: placebo = 38 (11) venlafaxine = 41 (12)		3. HAM-A scores
	4. Duration 28 weeks	4. Sex: 59% females		
	5. Analysis: LOCF	5. Setting: outpatients		
		6. History: excluded major depression; any psychotic disorder; clinically significant psychiatric disorder other than GAD		
Pollack 2001	1. Randomized	1. Diagnosis: GAD (DSM-IV)	1. Placebo (N = 163)	1. Dropout rates
	2. Double blind	2. N = 331	2. Paroxetine (N = 161)	2. CGI scores
	3. Two parallel groups	3. Age: placebo = 41.3(range 19-80); paroxetine =39.7(range19-69)		3. HAM-A scores
	4. Duration: 8 weeks	4. Sex: 66% females		4. Sheehan disability scale scores
	5. Analysis ITT	5. Setting: outpatients		
		6. History: DSM-IV criteria for GAD, MINI-International Neuropsychiatric Interview, Excluded any other Axis I disorder.		
Rickels 1993	1. Randomized	1. Diagnosis: GAD (DSM-III)	1. Placebo (N = 55)	1. Dropout rates
	2. Double blind	2. N = 230	2. Imipramine+/-143 mg/d (N = 58)	2. CGI scores
	3. Four parallel groups (placebo, imipramine, trazodone, diazepam)	3. Age: 39 (12)	3. Trazodone +/- 225 mg/d (N = 61)	3. HAM-A scores

e)

Table 1 – Characteristics of included studies (Continuation)

Study ID	Methods	Participants	Interventions	Outcomes
	4. Duration: 8 weeks	4. Sex: 61,4% females	4. Diazepam +/- 26 mg/d (N = 56)	
	5. Analysis: LOCF	5. Setting: outpatients		
		6. History: Gad without other significant axis I diagnoses		
Rickels 2000	1. Randomized	1. Diagnosis: GAD (DSM-IV)	1. Placebo (N = 96)	1. Dropout rates
	2. Double-blind	2. N = 377	2. Venlafaxine 75 mg/d (N = 86)	2. CGI scores
	3. Four parallel groups	3. Age: placebo = 40.9 (11.3); venlafaxine 75 = 40.4 (12.8); venlafaxine 150 = 39.6 (11.9); venlafaxine 225 = 42.4 (12.3)	3. Venlafaxine 150 mg/d (N = 81)	3. HAM-A scores
	4. Duration 8 weeks	4. Sex: 56% females	4. Venlafaxine 225 mg/d (N = 86)	4. Hospital Anxiety and depression Scale anxiety subscale
	5. Analysis: LOCF	5. Setting: outpatients		
		6. History: DSM-IV criteria for GAD but not for Major Depressive Disorder		
Rocca 1997	1. Randomized	1. Diagnosis: GAD (DSM-IV)	1. Imipramine 50-100 mg/d (N = 26)	1. Dropout rates
	2. Double blind	2. N = 81	2. Paroxetine 20 mg/d (N = 30)	2. CGI scores
	3. Duration 8 weeks	3. Age: imipramine group (means and SD) = 37.6 (9.1); paroxetine 20 mg/d group = 35.3 (9.3)	3. Chlordesmethyldiazepam 4.2 (1.1) mg/d (N = 25)	3. HAM-A scores
	4. Three parallel groups	4. Sex: 57% females		
	5. Analysis: Repeated measures ANOVA (interaction drug x time)	5. Setting: outpatients		
		6. History: DSM-IV GAD (other Axis I diagnosis were excluded)		
Rynn 2001	1. Randomized (random study assignments were made in groups of four patients)	1. Diagnosis: GAD (DSM-IV, according to the Anxiety Disorders Interview Schedule for children-Revised)	1. Placebo (N = 11)	1. Dropout rates
	2. Double blind	2. N = 22	2. Sertraline (N = 11)	2. CGI scores
	3. Duration: 9 weeks	3. Age: 5 to 17		3. HAM-A scores
	4. Analysis: Repeated measures analysis of covariance (with baseline score on CGI as covariate	4. Sex: 33% female		
		5. Setting: outpatients		
		6. History: Included DSM-IV GAD patients; excluded unstable or acute medical conditions and additional axis I or II disorders (apart from subsyndromal symptoms of separation anxiety)		

Table 2 – Efficacy analysis: antidepressants x placebo (relative risk for non-response to antidepressant)

Antidepressant	Relative Risk (95% CI)	NNT (95% CI)	Non response rate in the placebo co group
Imipramine	0.67 (0.50-0.91)	4.0 (2.4-13.7)	75%
Venlafaxine	0.68 (0.46-0.99)	5.0 (3.58-8.62)	66%
Paroxetine	0.72 (0.56-0.92)	6.72 (3.9-24.7)	53%
Sertraline	0.10 (0.02-0.65)	1.22 (0.90-1.7)	90%
All antidepressants	0.70 (0.62-0.79)	5.5 (4.1-8.4)	62%

CI: Confidence interval
NMT Number needed to treat

Table 3 – Acceptability (dropouts): antidepressants x placebo

Antidepressant	Relative Risk (95% CI)
Imipramine	0.71 (0.41-1.24)
Venlafaxine	0.86 (0.72-1.02)
Paroxetine	1.15 (0.74-1.78)
Sertraline	0.45 (0.03-5.84)
All antidepressants	0.95 (0.84-1.09)

CI: Confidence interval

Discussion

1. Efficacy

The present review showed the efficacy of antidepressants in the treatment of GAD. These results were obtained when drugs with differential profiles such as imipramine and venlafaxine were compared to placebo. The calculated NNT for these antidepressants as a group, was 5.54. This means that about 6 patients have to be treated to cause one additional clinical improvement.

Imipramine showed a smaller NNT (4.07, 95% CI 2.39 to 13.74) than venlafaxine = 5.06 (95% CI 3.6 to 8.6) and paroxetine = 6.7 (95% CI 3.9 or 24.7). However, this does not allow for the conclusion that the effect size of imipramine is larger. Only one study compared an SSRI (paroxetine) to imipramine, and similar results were found for the efficacy assessment and acceptability. The available evidence clearly suggests that antidepressants are better than placebo. The idea that antidepressants may improve both symptoms of depression and anxiety is not a new one. However, this review was conducted using studies which included patients with GAD without concurrent major depression or other Axis I comorbidities. This allows to conclude that the anxiolytic effect of antidepressants in GAD is independent from its effect on major depression and dysthymia.

Only one study assessed the use of antidepressants among children and adolescents. This study included a small sample of patients (N = 22) and, therefore, results should be viewed with caution. However, the effect size obtained was very robust, which suggests that younger patients may have a more favourable response than adults. There is no evidence that one antidepressant is superior to any other. Additional clinical trials comparing different antidepressants are needed to address this issue.

2. Acceptability

Overall, the number of patients dropping out of studies was similar in the antidepressant and placebo groups. Newer antidepressants such as venlafaxine and paroxetine usually have a better acceptability profile than tricyclics. However, there was no difference between the tricyclic imipramine and the new antidepressants (venlafaxine and paroxetine) in terms of dropouts. Again, a direct comparison between venlafaxine and imipramine in terms of acceptability is lacking. Some insight into this question can be drawn from the study conducted by Rocca 1997,[17] which allowed a direct comparison between imipramine and the selective serotonin reuptake inhibitor (SSRI) paroxetine. In the latter study, similar rates of dropouts were reported, adding to the notion that acceptability may not vary as much as one might expect when newer, and supposedly better tolerated drugs, are compared to the tricyclics. The study conducted by Rocca 1997[17] cannot be used as a final argument in favour of an equal acceptability between tricyclics and SSRIs as the sample size of this study was rather small (25 patients allocated to paroxetine and 18 patients allocated to imipramine), wich may allow a type II error. However, the study conducted by Rocca 1997[17] is consistent with the side effect profile expected for these two classes of drugs. Paroxetine was associated with significantly more reports of nausea whereas imipramine was associated with more anti-cholinergic side effects such as dry mouth, constipation and drowsiness.

3. Generalizability of findings

The present review included only GAD patients without concurrent Axis I co-morbidities. This is a strength in terms of the generalizability of the findings for 'pure GAD' patients. However, if one considers that nearly all people (around 90%) with GAD also have psychiatric co-morbidities,[4] one should be cautious in translating findings obtained in such an specific (and unusual) population into clinical practice. However, the two major co-morbidities of GAD are major depression and dysthymia, both of which are known to be treatable with antidepressants, which suggest that antidepressants would probably be a reasonable treatment for GAD patients in the clinical context.

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