Pharmacotherapy of Panic Disorder: Differential Efficacy From a Clinical Viewpoint

Johan A. den Boer, M.D., Ph.D.

Antidepressants and high-potency benzodiazepines have been used to treat patients with panic disorder. This review considers the efficacy of these treatments in reducing panic attack frequency and in addition considers their ability to attenuate global anxiety, depressive symptomatology, agoraphobic avoidance, and overall impairment. An extensive database is available for the tricyclic antidepressants imipramine and clomipramine, the serotonin selective reuptake inhibitor paroxetine, and the benzodiazepine alprazolam. The antidepressants are more effective than the benzodiazepines in reducing associated depressive symptomatology and are at least as effective for improving anxiety, agoraphobia, and overall impairment. *(J Clin Psychiatry 1998;59[suppl 8]:30–36)*

Different antidepressant classes have been studied in the treatment of panic disorder, including the tricyclic antidepressants (TCAs), the monoamine oxidase inhibitors (MAOIs), and the serotonin selective reuptake inhibitors (SSRIs). In addition, high-potency benzodiazepines, notably alprazolam, have been studied. The efficacy data generated in controlled clinical trials will be reviewed in this paper. Different endpoint measures will be considered, including panic frequency, global anxiety, depressive symptomatology, agoraphobic avoidance, and overall impairment. A variety of assessment scales have been employed in panic disorder research, and not all studies have considered each of these domains. Nevertheless, a substantial database is now available in the literature that allows conclusions to be drawn on the relative efficacy of the various treatments. Controlled clinical studies reviewed in this paper were selected from a literature search of the full MEDLINE database (1966 to date) using the terms *panic disorder*, *clinical trial*, *placebo*, and *placebo-controlled* and from the author's own collection of publications.

PANIC FREQUENCY

The most stringent efficacy criterion for assessing reduction in panic frequency is the proportion of patients who become free from panic attacks at endpoint. This measure will be considered in this section.

Proportion of Patients Achieving a Panic-Free State

Data are available on the proportion of patients free from panic attacks at the end of treatment with SSRIs, TCAs, or benzodiazepines (Table 1). For the MAOIs, no controlled data have been identified for this endpoint.

SSRIs. Percentages of patients who achieved a panic-free state through treatment with the SSRIs paroxetine, fluvoxamine, and citalopram have been reported in placebo-controlled studies. Paroxetine studies comprise the largest data set: over 700 patients have been treated for periods ranging from 10 to 36 weeks.[3–6] After acute treatment, panic-free rates of 36% to 86% were observed for paroxetine and 16% to 50% for placebo; in the placebo-controlled comparison with clomipramine, the percentage of panic-free patients was 51% for paroxetine and 37% for clomipramine.[4] In 2 small studies, up to 73% of patients treated with fluvoxamine were panic-free at endpoint[1,2] compared with a modest placebo response rate of approximately 25%. Citalopram and clomipramine have recently been compared by Wade et al.[7] At the most effective citalopram dose (20–30 mg/day), approximately 58% of patients were panic-free compared with 50% of patients receiving clomipramine and 32% of placebo patients.

TCAs. In the Cross National Collaborative Study,[8] one of the largest studies ever conducted in panic disorder, over 1000 patients were randomly assigned to receive 8 weeks of treatment with either imipramine, alprazolam, or placebo; rates of panic-free patients of 70% were reported for both active treatments compared with 50% for placebo group. Two further placebo-controlled comparisons[9,10] reported rates of panic-free patients of 61% and 44% for imipramine and 68% and 57% for alprazolam. There was no difference

From the Psychiatric University Clinic, Academic Hospital Groningen, Groningen, The Netherlands.

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Reprint requests to: Johan A. den Boer, M.D., Ph.D., Psychiatric University Clinic, Academic Hospital Groningen, Hanzeplein 1, P.O. Box 30.001, 9700 RB Groningen, The Netherlands.

Table 1. Percentage of Patients Free From Panic Attacks at Endpoint*

Study	Duration (wk)	N	Percentage Panic-Free		
Placebo-Controlled Studies of SSRIs and Clomipramine			SSRI	Clomipramine	Placebo
Fluvoxamine					
Hoehn-Saric et al[1]	8	50	61%[a]	…	22%
Black et al[2]	8	75	73%[a]	…	25%
Paroxetine					
Oehrberg et al[3b]	12	120	36%[a]	…	16%
Lecrubier et al[4]	12	367	51%[a]	37%	32%
Lecrubier et al[5]	36	176	85%[a]	72%	59%
Ballenger et al[6]	10	278	86%[a]	…	50%
Citalopram					
Wade et al[7]	8	475	43%–58%[a]	50%[a]	32%
Comparative Studies of Alprazolam and Imipramine			Imipramine	Alprazolam	Placebo
Cross National Collaborative Panic Study[8]	8	1168	70%[a]	70%[a]	50%
Schweizer et al[9]	8	106	44%[c]	57%[b]	29%
Andersch et al[10]	8	123	61%[a]	68%[a]	34%
Placebo-Controlled Studies of Alprazolam				Alprazolam	Placebo
Ballenger et al[11]	8	481		59%[a]	50%
Pecknold et al[12]	8	126		60%	43%
Tesar et al[13]	6	72		46%[a]	14%
Munjack et al[14]	5	64		75%[b]	44%
Lydiard et al[15]	6	94		65%[a]	15%
Noyes et al[16]	8	241		71%[a]	38%

*Abbreviation: SSRI = serotonin selective reuptake inhibitor.
[a]Significantly different from placebo.
[b]One or zero attacks in a 3-week period.
[c]$p < .06$.

between the active treatments in any of these studies. Modigh and colleagues[17] reported that clomipramine was more effective than imipramine in a small study of 68 patients, reporting 100% of the clomipramine-treated patients to be panic-free at the end of a 12-week study; the rate for imipramine was not given. A comparison of lofepramine and clomipramine conducted in 66 patients in Ireland[18] reported that approximately 70% of patients in the active treatment groups and 42% of those taking placebo became panic-free.

Benzodiazepines. Although there is a substantial database relating to the efficacy of alprazolam in the treatment of panic disorder, many studies do not report the proportion of patients free from panic attacks at endpoint. In the placebo-controlled comparisons that have assessed this endpoint, rates of panic-free patients in the range of 46% to 75% were recorded.[11–16] Comparative trials of benzodiazepines and TCAs in panic disorder have already been discussed above. Gould et al.[19] conducted a meta-analysis of treatment studies for panic disorder including only those studies that employed a control group. They identified only 7 studies with pharmacologic treatment that reported rates of panic-free patients and calculated that the rate for benzodiazepines was 61% and for antidepressants was 58%, a difference that was not statistically significant.

Long-term studies. Data on the proportion of patients free from panic at endpoint are available for alprazolam, imipramine, clomipramine, and paroxetine. Burrows et al.[20] reported a rate of panic-free patients of 70% with alprazolam in an 8-month study, while Marchesi et al.[21] recently reported a 75% rate in a 1-year study with imipramine. In a 9-month extension of an acute treatment study with paroxetine,[4] the proportion of patients who became free of panic attacks continued to increase, and at study endpoint, 85% of paroxetine patients were panic-free compared with 72% of clomipramine patients.[5] For further discussion of the long-term treatment of panic disorder, see the paper by J. R. T. Davidson in this supplement.

GLOBAL ANXIETY

The efficacy of pharmacotherapy in reducing global anxiety levels in patients with panic disorder has been assessed with a variety of rating scales. The Hamilton Rating Scale for Anxiety (HAM-A) is most frequently employed, but instruments such as the Symptom Checklist-90 (SCL-90) and the Clinical Anxiety Scale have also been used. For this endpoint measure, data are available for benzodiazepines, MAOIs, TCAs, and SSRIs (Table 2).

MAOIs

Significant reductions in global anxiety levels have been reported after acute treatment with phenelzine[22] and brofaromine.[23,24,28] In 2 of the studies,[22,23] a TCA comparator was included in the study, and in 1 study,[28] the SSRI fluvoxamine; no difference between active treatment groups was noted.

SSRIs

Reductions in global anxiety ratings have been demonstrated after treatment with paroxetine[3–6] or fluvoxamine.[1,2,25–27,31] Both SSRIs are reported to have comparable efficacy to clomipramine with respect to this endpoint measure.[4,25] Citalopram and clomipramine both were found to reduce anxiety levels in a large multicenter comparative study,[7] with no difference in efficacy between them. Limited data are available with the other SSRIs; fluoxetine was compared with desipramine in a small 10-week study and found to reduce anxiety levels,[30] while a placebo-controlled trial with sertraline has been presented at an international meeting, and a significant reduction in HAM-A scores over and above placebo was displayed.[29]

TCAs

The TCAs imipramine and clomipramine have often been included as active comparators when investigating antidepressants in the treatment of panic disorder. In addition to the comparative trials with MAOIs and SSRIs already discussed, there have been comparisons within the TCA class. Clomipramine was reported to be significantly

Table 2. The Effect of Pharmacotherapy on Global Anxiety Level*

Study	Duration (wk)	N	Scores		
			MAOI	TCA	Placebo
Phenelzine					
Sheehan et al[22]	12	57			
SCL-90 Anxiety baseline			2.45	2.59	2.58
SCL-90 Anxiety endpoint			0.96	1.04	2.02
Brofaromine					
Bakish et al[23]	8	93			
HAM-A baseline			17	18	…
HAM-A endpoint			12.5	8	…
Van Vliet et al[24]	12	30			
HAM-A baseline			26	…	24
HAM-A endpoint			15	…	23
			SSRI	Active Comparator	Placebo
Paroxetine					
Oehrberg et al[3]	12	120			
HAM-A baseline			24.3	…	23.5
HAM-A endpoint			9.4	…	13.5
Ballenger et al[6]	10	278			
HAM-A baseline			19.0	…	19.7
HAM-A endpoint			8.5	…	13.1
Lecrubier et al[4]	12	367			
HAM-A % patients with 50% reduction from baseline			55.5%	51.2%	35.2%
Fluvoxamine					
den Boer et al[25]	6	50			
HAM-A baseline			22	21	…
HAM-A endpoint			9	9	…
den Boer and Westenberg[26]	6	44			
HAM-A baseline			22	…	…
HAM-A endpoint			12	…	…
den Boer and Westenberg[27]	8	60			
HAM-A baseline			25	…	24
HAM-A endpoint			10	…	21
Black et al[2]	8	75			
CAS baseline			13.7	…	14.6
CAS endpoint			4.9	…	10.8
Hoehn-Saric et al[1]	8	50			
CAS baseline			11	…	10
CAS endpoint			4	…	8
Van Vliet et al[28]	12	30			
HAM-A baseline			24	26	…
HAM-A endpoint			14	14	…
Sertraline					
Baumel et al[29]					
HAM-A change from baseline	10	168	–12.1	…	–9.4
Citalopram					
Wade et al[7]	8	475			
HAM-A baseline			22.9	24.2	23.0
HAM-A endpoint			12.3	12.7	15.6
Fluoxetine					
Bystritsky et al[30,a]	10	22			
HAM-A baseline			23	23	…
HAM-A endpoint			8	15	…

*Abbreviations: CAS = Clinical Anxiety Scale, HAM-A = Hamilton Rating Scale for Anxiety, MAOI = monoamine oxidase inhibitor, TCA = tricyclic antidepressant.
[a]Desipramine was the comparator in this study, not clomipramine.

more effective than imipramine in reducing global anxiety,[17] although this has to be considered in the light of the finding that clomipramine did not produce a significant response over and above placebo in this same study. Lofepramine has been compared with clomipramine in panic disorder and found to be less effective in reducing global anxiety.[18]

Benzodiazepines

Alprazolam,[15,16,32] diazepam,[16] and clonazepam[33] can all reduce global anxiety levels in patients with panic and have shown superiority over placebo. The relative efficacy of high-potency benzodiazepines and antidepressants has been investigated in a number of meta-analyses, 2 of which have considered global anxiety ratings.[34,35] In both analyses, the antidepressants and benzodiazepines were comparable with respect to the reduction in global anxiety.

DEPRESSIVE SYMPTOMATOLOGY

Depressive symptomatology is associated with panic disorder in a substantial proportion of patients. Clinical trials have assessed improvements in depression by the inclusion of appropriate rating scales (predominantly the Hamilton Rating Scale for Depression [HAM-D] and Montgomery-Asberg Depression Rating Scale, although the Zung Self-Rating Depression Scale has also been used). Variations in the inclusion criteria for patients in the clinical studies reviewed in this paper that relate to the presence of comorbid depression are apparent. In a number of the fluvoxamine studies,[24–28] patients were excluded if they had a HAM-D score of 15 or greater, whereas in the study of Keller and colleagues,[36] patients with comorbid major depression were included. Baseline and endpoint data for all the clinical studies reviewed are presented in Table 3 and allow the reader to assess the level of depressive symptomatology present in the patient population at baseline. Data for all 4 drug groups considered in this review are available (Table 3).

MAOIs

Phenelzine[22] and brofaromine[23,24] both have demonstrated their effectiveness in improving depressive symptoms in panic patients. Sheehan et al.[22] found no difference in efficacy between phenelzine and imipramine, whereas Bakish and colleagues[23] stated that brofaromine was less effective than clomipramine in reducing the mean HAM-D score.

SSRIs

Controlled clinical studies with paroxetine[5,6] and fluvoxamine[1,2,25,27] have shown their efficacy in improving depressive symptomatology. Fluoxetine[30] and citalopram[7]

Table 3. The Effect of Pharmacotherapy on Depressive Symptomatology Scores*

Study	Scores		
	MAOI	TCA	Placebo
Phenelzine			
Sheehan et al[22]			
Zung SDS baseline	62.1	65.4	63.0
Zung SDS endpoint	45.4	51.1	57.7
Brofaromine			
Van Vliet et al[24]			
MADRS baseline	9.9	…	10.1
MADRS endpoint	6.7	…	10.3
	SSRI	TCA	Placebo
Paroxetine			
Ballenger et al[6]			
HAM-D baseline	13.9	…	12.9
HAM-D endpoint	6.0	…	9.2
Lecrubier et al[4a]			
MADRS baseline	13.1	12.7	13.4
MADRS endpoint	8.4	7.2	10.2
Lecrubier et al[5a]			
MADRS baseline	13.5	12.7	12.1
MADRS endpoint	4.0	4.3	6.7
Fluvoxamine			
Black et al[2]			
MADRS baseline	14.0	…	16.9
MADRS endpoint	6.3	…	12.1
Hoehn-Saric et al[1]			
MADRS baseline	10	…	9
MADRS endpoint	3	…	7
den Boer et al[25]			
HAM-D baseline	11	11	…
HAM-D endpoint	6	4.5	…
den Boer and Westenberg[26]			
HAM-D baseline	11	11	…
HAM-D endpoint	6	7	…
den Boer and Westenberg[27]			
HAM-D baseline	11.3	…	10.8
HAM-D endpoint	5.2	…	9.7
Fluoxetine			
Bystritsky et al[30]			
HAM-D baseline	16	17	…
HAM-D endpoint	7	10	…
Citalopram			
Wade et al[7]			
MADRS baseline	11.4	12.9	11.9
MADRS endpoint	6.5	6.9	9.5
	Benzodiazepine	TCA	Placebo
Alprazolam			
Cross National Collaborative Study[8]			
HAM-D baseline	13.9	14.0	14.4
HAM-D endpoint	7.4	6.8	9.4
Keller et al[36]			
HAM-D baseline	19.7	21.1	22.0
HAM-D endpoint	9.0	8.8	13.6

*Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, Zung SDS = Zung Self-Rating Depression Scale.
[a]Data on file, SmithKline Beecham.

have also been reported to improve depressive symptoms in panic disorder patients, although the database, in particular with fluoxetine, is considerably smaller. Comparative data with clomipramine exist for paroxetine,[4,5] fluvoxamine,[25,26] and citalopram[7]; in no case was there any significant difference in efficacy between the SSRI and the TCA. Similarly, there was no evidence for any difference in efficacy between fluoxetine and desipramine.[30]

TCAs

The TCAs, predominantly imipramine and clomipramine, have demonstrated efficacy in the treatment of depressive symptomatology not only in the studies cited above with MAOIs and SSRIs, but also in comparison with high-potency benzodiazepines (e.g., Cross National Collaborative Study,[8] Keller et al.[36]). There is no evidence to support any difference in efficacy between the TCAs, SSRIs, and MAOIs in treating the depressive symptomatology associated with panic disorder, although meta-analyses have indicated differences in efficacy between the TCAs and the benzodiazepines (see below).

Benzodiazepines

Benzodiazepines do not have an indication for depression, although there is some evidence that both alprazolam[8,32,36] and clonazepam[33] have reduced depressive symptoms, compared with placebo, in controlled studies. However, meta-analyses comparing benzodiazepines with TCAs in particular[34] or antidepressants in general[35,37] have consistently shown them to be less effective in the treatment of depressive symptoms than antidepressants.

AGORAPHOBIC AVOIDANCE

The next domain to be considered is that of agoraphobic avoidance. There are considerable differences in the methodology used to assess this endpoint: the SCL-90, the Overall Phobia Scale, the Marks Matthews Phobia Scale, the Marks Sheehan Phobia Scale, the agoraphobia item on the Fear Questionnaire, and the Clinical Global Impressions scale (CGI) have all been employed. While this makes it virtually impossible to make comparisons across studies, within-trial comparisons between the TCAs and the SSRIs, MAOIs, and benzodiazepines are possible (Table 4).

MAOIs

Phenelzine[22] and brofaromine[23,24,28] both have reduced agoraphobic avoidance in panic patients, although at endpoint, avoidance behavior was still evident. In comparisons with imipramine,[22] clomipramine,[23] and fluvoxamine,[28] comparable efficacy for this endpoint was observed.

SSRIs

Paroxetine and clomipramine produced similar reductions in overall phobia scores (Marks Sheehan Phobia Scale) during a 12-week treatment period, while minimal change was recorded in the placebo group.[4] Further improvements in phobic avoidance with both active treatments were evident during the long-term extension of this study.[5] No separation between the active treatment groups

Table 4. The Effect of Pharmacotherapy on Agoraphobia Scores*

Study	Scores			
	Benzodiazepine	TCA	MAOI	Placebo
Phenelzine				
Sheehan et al[22]				
SCL-90 phobic anxiety baseline	…	2.7	2.8	3.0
SCL-90 phobic anxiety endpoint	…	1.3	1.1	2.4
Brofaromine				
Bakish et al[23]				
MMPS baseline	…	14	6	…
MMPS endpoint	…	6	3	…
Van Vliet et al[24]				
Fear Questionnaire baseline	…	…	31	35
Fear Questionnaire endpoint	…	…	24	35
Alprazolam				
Keller et al[36]				
Overall Phobia score baseline	6.9	7.4	…	6.6
Overall Phobia score endpoint	3.7	3.8	…	4.5
	SSRI	Active Comparator		Placebo
Paroxetine				
Lecrubier et al[4]				
MSPS overall phobia score change from baseline	–2.5	–2.4		–1.4
Ballenger et al[6]				
MSPS fear score baseline	7.0	…		6.6
MSPS fear score endpoint	3.4	…		4.8
Fluvoxamine				
den Boer et al[25]				
SCL-90 phobic anxiety baseline	1.7	1.9		…
SCL-90 phobic anxiety endpoint	1.2	0.7		…
den Boer and Westenberg[26]				
SCL-90 phobic anxiety baseline	2.9	3.3		…
SCL-90 phobic anxiety endpoint	2.3	1.8		…
den Boer and Westenberg[27]				
Fear Questionnaire baseline	35.8	…		29.8
Fear Questionnaire endpoint	23.8	…		28.8
Van Vliet et al[28]				
Fear Questionnaire baseline	30	30		…
Fear Questionnaire endpoint	22	21		…
Fluoxetine				
Bystritsky et al[30]				
CGI phobic avoidance baseline	4	5		…
CGI phobic avoidance endpoint	2	3		…

*Abbreviations: CGI = Clinical Global Impressions scale, MMPS = Marks Matthews Phobia Scale, MSPS = Marks Sheehan Phobia Scale, SCL-90 = Symptom Checklist-90.

occurred either in the short- or long-term. Improvements in phobic fear were noted as early as 4 weeks after the initiation of paroxetine treatment in a recent study reported by Ballenger and colleagues.[6]

The effect of fluvoxamine on agoraphobic avoidance was assessed using the phobic anxiety subscale of the SCL-90 in 2 studies conducted in the 1980s[25,26] and by use of the Fear Questionnaire in later studies.[27,28] In all cases, there was a diminution of agoraphobic behavior, although at endpoint, the patients were still exhibiting signs of avoidance. Active comparators in the fluvoxamine studies included clomipramine,[25] which was statistically superior to fluvoxamine; maprotiline,[26] which produced only a small reduction in phobic anxiety; and brofaromine (see previous sections). Data for the other SSRIs are either not in the public domain or, in the case of fluoxetine, limited. Bystritsky et al.[30] assessed the CGI phobic avoidance item and showed that both fluoxetine and desipramine reduced the score.

TCAs

Comparative data for clomipramine and imipramine with the MAOIs and SSRIs (see earlier) indicate that both TCAs are effective in reducing agoraphobic avoidance. In a comparison between imipramine and alprazolam conducted by Keller et al.,[36] both active treatments were equally efficacious, compared with placebo, in reducing overall phobia, fear of phobia, and avoidance of phobia, although an earlier onset of effect was noted with alprazolam. In contrast to these results, Fahy and colleagues[18] reported no effect of either lofepramine or clomipramine on a self-rated Fear Inventory.

Benzodiazepines

Subjects receiving alprazolam[15,16,32,36] and diazepam[16] are reported to experience significantly greater reductions in phobic symptoms than those taking placebo. Comparisons with antidepressants have been undertaken (e.g., Keller et al.[36]), and 3 meta-analyses have compared effect sizes between the benzodiazepines and antidepressants.[34,35,37] In the two older meta-analyses, the number of studies involved was too small to make valid comparisons between treatments. Van Balkom and colleagues,[35] however, included 17 studies with high-potency benzodiazepines and 15 studies with antidepressants, reporting effect sizes of 1.00 and 1.02, respectively. Both active treatments were significantly different from the control condition, but there was no separation between the treatments.

OVERALL IMPAIRMENT

The final domain to be considered in this review is that of overall impairment. Many studies, especially those conducted in the 1980s, did not include this endpoint measure in their study design and therefore the dataset is substantially smaller. The Sheehan Disability Scale was employed in the vast majority of the studies.

MAOIs

The work and social disability of patients receiving phenelzine and imipramine was assessed in the study by Sheehan et al.[22] Both active treatments improved functional disability compared with placebo, and when the 2 active treatments were compared, there was a significant difference in favor of phenelzine.

SSRIs

An assessment of overall impairment has been included in clinical trials conducted with paroxetine[4,5] and fluvox-

amine.[1,2] In both the short- and long-term comparison of paroxetine and clomipramine, improvements in work, social, and family life were noted for both active treatments compared with placebo.[4,5] Throughout the long-term trial, patients continued to improve with respect to their daily functioning.[5] Reductions in the impairment associated with work, social, and family life have been observed after treatment with fluvoxamine in placebo-controlled trials.[1,2]

TCAs

In the Cross National Collaborative Study,[8] the percentage of patients who required changes in their social functioning at the end of treatment was assessed for imipramine, alprazolam, and placebo. At baseline, approximately 24% of patients in each treatment group required a change in their social functioning; this reduced to 6%, 4%, and 15% in the imipramine, alprazolam, and placebo groups, respectively, at study endpoint—a difference that was significant for both active treatments. Comparison between imipramine and alprazolam has also been conducted by Keller et al.,[36] who found that both active treatments reduced the work and social impairment associated with panic disorder.

Benzodiazepines

In addition to the comparative studies cited above, a number of other studies have reported an improvement in work and/or social disability ratings after treatment with alprazolam[15,16,32] and diazepam.[16]

CONCLUSIONS

Controlled efficacy data are available for the antidepressants (MAOIs, SSRIs, and TCAs) and the high-potency benzodiazepines in the treatment of panic disorder. For the most stringent efficacy criterion, attainment of a panic-free state, data are available for the TCAs (clomipramine and imipramine), the SSRIs (paroxetine, fluvoxamine, and citalopram), and alprazolam. No data have been identified with the MAOIs. Long-term efficacy data are only available for the TCAs imipramine and clomipramine, the SSRI paroxetine, and the benzodiazepine alprazolam. The effect of the various drug treatments on associated anxiety, depression, agoraphobic avoidance, and overall impairment has been considered. The antidepressants have been shown to be more effective than the benzodiazepines in treating depressive symptomatology and at least as effective in improving anxiety, agoraphobic avoidance, and overall impairment.

Drug names: alprazolam (Xanax), clomipramine (Anafranil), clonazepam (Klonopin), desipramine (Norpramin and others), diazepam (Valium and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), maprotiline (Ludiomil), paroxetine (Paxil), phenelzine (Nardil).

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