BMC Psychiatry

Research article

Three year naturalistic outcome study of panic disorder patients treated with paroxetine

Pinhas N Dannon*[1,2], Iulian Iancu[1], Ami Cohen[2], Katherine Lowengrub[1], Leon Grunhaus[2] and Moshe Kotler[1]

Address: [1]The Rehovot Community Mental Health Care & Rehabilitation Center affiliated to Tel Aviv University, 76449, Rehovot, Israel and [2]The Chaim Sheba Med Center affiliated to Tel Aviv University, 52621, Tel Hashomer, Israel

Email: Pinhas N Dannon* - pinhasd@post.tau.ac.il; Iulian Iancu - iulian1@bezeq.int.il; Ami Cohen - cohenami@hotmail.com; Katherine Lowengrub - rephas@int.gov.il; Leon Grunhaus - grunhausl@sheba.health.gov.il; Moshe Kotler - rephas@int.gov.il

* Corresponding author

Published: 11 June 2004

BMC Psychiatry 2004, **4**:16

Received: 05 November 2003
Accepted: 11 June 2004

This article is available from: http://www.biomedcentral.com/1471-244X/4/16

Abstract

Background: This naturalistic open label follow-up study had three objectives:

1) To observe the course of illness in Panic Disorder patients receiving long-term versus intermediate-term paroxetine treatment

2) To compare the relapse rates and side-effect profile after long-term paroxetine treatment between patients with Panic Disorder and Panic Disorder with Agoraphobia.

3) To observe paroxetine's tolerability over a 24 month period.

Methods: 143 patients with panic disorder (PD), with or without agoraphobia, successfully finished a short-term (ie 12 week) trial of paroxetine treatment. All patients then continued to receive paroxetine maintenance therapy for a total of 12 months. At the end of this period, 72 of the patients chose to discontinue paroxetine pharmacotherapy and agreed to be monitored throughout a one year discontinuation follow-up phase. The remaining 71 patients continued on paroxetine for an additional 12 months and then were monitored, as in the first group, for another year while medication-free. The primary limitation of our study is that the subgroups of patients receiving 12 versus 24 months of maintenance paroxetine therapy were selected according to individual patient preference and therefore were not assigned in a randomized manner.

Results: Only 21 of 143 patients (14%) relapsed during the one year medication discontinuation follow-up phase. There were no significant differences in relapse rates between the patients who received intermediate-term (up to 12 months) paroxetine and those who chose the long-term course (24 month paroxetine treatment). 43 patients (30.1%) reported sexual dysfunction. The patients exhibited an average weight gain of 5.06 kg. All patients who eventually relapsed demonstrated significantly greater weight increase (7.3 kg) during the treatment phase.

Conclusions: The extension of paroxetine maintenance treatment from 12 to 24 months did not seem to further decrease the risk of relapse after medication discontinuation. Twenty-four month paroxetine treatment is accompanied by sexual side effects and weight gain similar to those observed in twelve month treatment.

Background

Panic Disorder (PD) is considered to be a chronic debilitating illness, which is characterized by recurrent, severe and apparently spontaneous anxiety attacks accompanied by autonomic symptoms [1]. This disorder constitutes a major health problem with significant costs not only for the individual but for the health service system as well [2]. PD has an estimated lifetime prevalence of about 3–5% [1]. The most common therapeutic interventions are Cognitive Behavioral Therapy [3] and pharmacotherapy [4,5]. Pharmacological treatments for PD have centered mainly on benzodiazepines and antidepressants [4,6,7]. Benzodiazepines have shown to be effective with rapid onset of action [8]. The long-term use of benzodiazepines, however, may be associated with the development of physiological dependence and withdrawal symptoms [2]. Studies with tricyclic agents and monoamine oxidase inhibitors (MAOIs) [9,10] have demonstrated good efficacy in the treatment of PD. Selective sertonin reuptake inhibitors (SSRIs), however, are better tolerated than the older agents with fewer side-effects and so have become the treatment of choice for PD [11]. Numerous controlled studies have demonstrated the effectiveness of these drugs [12-14].

Paroxetine was the first SSRI approved for treatment of PD [15], and its efficacy is well established in the short-term treatment of patients with PD [16,17]. According to the current APA practice guidelines for the treatment of PD, it is recommended to continue SSRI pharmacotherapy for one year despite a paucity of data examining the comparative efficacy of long-term (>12 months) treatment [11]. The optimal continuation period of paroxetine treatment to prevent future relapse is unclear.

Paroxetine treatment involves relatively high cost to the patients and to the health services. Long-term paroxetine treatment is associated with adverse effects such as sexual dysfunction and weight gain [5]. Lately, two studies have reported that adverse effects on sexual function occur in up to 75% of patients treated with paroxetine [6,18].

In this naturalistically designed follow-up study we address the following questions:

1) Does long term paroxetine treatment for up to 24 months will prevent relapse more effectively than twelve months of treatment?

2) What is the course of PD versus PD with agoraphobia?

3) What is the prevalence of sexual dysfunction and weight gain in long-term paroxetine treatment?

Methods

Patients

Over one hundred and eighty patients passing diagnostic screening for a diagnosis of PD or PDA were entered into a short-term (12 week) treatment phase in which they received paroxetine pharmacotherapy. 143 patients (78 women and 65 men; average age = 39.2 ± 9.2) showed an improvement in panic symptoms after the short-term treatment phase and entered a one year maintenance phase. All patients who entered the maintenance phase met the DSM-IV criteria for PD (n = 85) or PDA (n = 58). 17 patients had a history of prior drug or alcohol abuse. Exclusion criteria included the presence of a comorbid axis I diagnosis, long-term benzodiazepine use (>12 months), current substance abuse, and prior non-response to paroxetine therapy. Patients were generally physically healthy, although our patient sample included 11 patients with cardiovascular disease, 4 patients with hypertension, and 4 patients with non-insulin dependent diabetes mellitus. Twenty-seven (19%) of the patients had family history of anxiety disorders. 70% of our patients developed the onset of panic disorder between ages 20–40 and the remainder between ages 41–75. The majority of patients in our study (68%) were referred to us after a first episode of panic disorder.

Study design

This naturalistic outcome study was conducted at Sheba Medical Center in Israel. The participants were referred to the hospital's psychiatry ward either by an ER physician or by a family physician. All patients gave their informed consent for participating in the study. After an initial evaluation that included a semi-structured psychiatric interview and Panic Self Questionnaire (PSQ), all patients received paroxetine at an initial starting dose of 10 mg/day for one week and then 20 mg/day for one month. After one month of 20 mg/day paroxetine therapy, the dose was either maintained at 20 mg/day or increased to 40 mg/day according to individual patient response. 67/143 responders received adjunctive benzodiazepine therapy with either clonazepam (n = 42) or lorazepam (n = 25) during the first eight to twelve weeks of treatment. Note that clonazepam was given at a dose of 0.5–1.5 mg/day and lorazepam was given at a dose of 1–3 mg/day. After approximately 8–9 weeks of adjunctive benzodiazepine therapy, the benzodiazepines were gradually tapered and discontinued over a three week period. After week 12 of the study, none of our study patients continued to receive adjunctive benzodiazepine therapy. Note that the primary care physician of each patient was contacted to explain that the patients should not receive adjunctive benzodiazepines during the maintenance phase and medication discontinuation follow-up phase of the study. By week 12 of the study, all 143 responders

Table 1: Demographics and baseline measurements (N:143)*

	Intermediate treatment	Long term treatment	p
	X ± SD	X ± SD	
	(N = 72)	(N = 71)	
Age (y)	38.7 ± 9.6	39.6 + 8.9	NS
Gender (F/M)	39/33	41/30	NS
Age group (≤50, >50)	62/10	61/10	NS
Diagnosis (PD/PD and Agoraphobia)	48/24	37/34	NS
Past history of drug/alcohol abuse	12	5	NS
Comorbid physical problems	5	6	NS
Weight (baseline)	66.9 ± 8.8	65.2 ± 7.9	NS
PSQ (Number of panic attacks/w)	5.9 ± 1.4	6.2 ± 1.4	NS

* *Explanation: intermediate = 12 months long-term => 12 months*

entered into the one year maintenance phase in which they received paroxetine monotherapy.

After one year of paroxetine maintenance therapy, 127/143 (89%) patients were considered full responders, and 16/143 patients had a partial response to treatment (1–2 panic attacks per week). Full response was defined as complete absence of panic attacks including the absence of limited symptom attacks. At this point all of the patients were offered the choice of either: 1) medication taper and discontinuation or 2) continuing paroxetine pharmacotherapy for an additional year. An equal possibility to taper medication was offered to all patients. A subgroup of 72 full responders elected to taper and discontinue medication treatment. These patients remained under psychiatric supervision and were monitored in either the out-patient clinic or through telephone calls every two months, for a period of 6–12 months (average of 11 months). The evaluations made at the last clinical visit of each patient were regarded as the patient's final assessment. The remaining 71 patients (including 55 full responders and 16 partial responders) elected to continue paroxetine treatment for an additional year. After this additional period, these patients were also tapered off paroxetine and were followed medication-free for one year with clinical visits or telephone calls bimonthly.

Assessments of relapse and side-effects

Evaluations of the patient's condition were conducted at baseline and every 2 months, until the end of the study, and were based on the Panic Self-Questionnaire (PSQ) [19]. Relapse was defined as the occurrence of at least one panic attack after discontinuation of paroxetine treatment.

In accordance with previous studies, we monitored [1,3,20] weight gain and sexual dysfunction, for these are considered to be the most bothersome side effects of subacute and long-term paroxetine treatment. All patients were weighed at baseline before starting paroxetine therapy and then again at the end of maintenance therapy. Weight change was calculated by subtracting the weight at the baseline visit from the weight at their last clinical visit. Sexual disturbances were assessed clinically, in both men and women, with questions exploring sexual desire and sexual dysfunction. We note that a structured interview regarding sexual symptoms was not used.

Statistics

Statistical analysis was performed with t-test and ANOVA and ANOVA with repeated measures and χ^2. Levels of significance were set to .05 unless otherwise stated.

Results

Demographic and baseline versus endpoint measurements are summarized in tables 1, 2

Relapse

We defined relapse as the occurrence of a single panic attack after discontinuation of pharmacotherapy. 21/127 patients (17%) who entered the maintenance phase experienced one or more panic attacks during the one year follow-up period after paroxetine discontinuation. In the intermediate-term treatment group (12 months), the number of patients experiencing relapse was 13/72 (18%) as opposed to 8/55 (15%) in the long-term treatment group (24 months). The difference in relapse rates between the intermediate and long-term treatment groups was not statistically significant (df 1; $\chi^2 = 3.78$; $P > 0.05$). There were no significant differences in relapse rate between patients according to age, gender, or presence of

Table 2: Assessments at the end of maintenance therapy

	Intermediate treatment	Long-term treatment	t	CI	X2	p
	N = 72	N = 55				
Relapse*	13 (18%)	8 (15%)				NS
Weight gain	4.7 ± 3.9	5.2 ± 3.4				NS
Sexual dysfunction	21 (29%)	18 (33%)				NS
PSQ (Number of panic attacks/w)*	0.22 ± 0.7	0.23 ± 0.2				NS

**assessment made at the end of one year follow-up after medication discontinuation*

agoraphobia. The relapse rate of both the patients with drug and/or alcohol abuse did not differ from the rest (NS). Among the 67 patients who received benzodiazepines in addition to the paroxetine treatment, 13 (20%) relapsed, and the increased relapse rate in this group was statistically significant. (df 1; $\chi^2 = 4.74$; $P < 0.05$).

Common side effects

Weight gain

Body weight among the study population increased by 5.06 ± 3.66 kg from a mean weight of 66.1 ± 8.4 kg at the onset of treatment. This increase was statistically significant (t = -16.54; CI = -5.67, -4.46; P < 0.01). The relapsing patients gained significantly more weight (7.3 ± 6.9) than the fully recovered (4.9 ± 3.3) (t = 2.203; CI = -4.75, 0; P < 0.05). Weight gain was significantly greater among the patients who received benzodiazepines (t = 3.07; CI = -3.79, 0.80; P < 0.01) and among those over age 50 (t = 2.29; CI = 0.27, 3.71; P < 0.05).

No significant difference in the amount of weight gain was observed between the patients who completed 12 months of paroxetine treatment and the patients who continued the medication for more than 12 months. There were no significant differences in weight gain between patients according to gender, the use of drugs/alcohol, or the presence of agoraphobia.

Sexual side-effects

43 out of the 143 patients (30%) reported sexual impairment. The prevalence of sexual side effects did not differ between the patients who completed 12 months of paroxetine treatment (29%) and the patients who received paroxetine for more than 12 months (33%) (df 1, $\chi^2 = 0.56$, $P > 0.05$). Sexual side effects did not differ significantly according to gender, age, or past history of drug and/or alcohol use (NS). However, sexual side effects were substantially more common in patients who suffered from PD with agoraphobia (41%) than in patients who suffered from PD (22%) (df 1, $\chi^2 = 5.93$, $P < 0.02$).

PD versus PD with agoraphobia

Patients suffering from PD with agoraphobia had more attacks per week at the onset time of treatment (6.5+1.4) in comparison to the PD without agoraphobia patients (5.8+1.3) (t = 3.00; CI = -1.13, -0.23 ; P < 0.05).

In addition, 36/58 patients suffering from PD with agoraphobia (62.1%) required benzodiazepine augmentation compared with 31/85 (36.5%) among the patients with PD alone (df 1; $\chi^2 = 9.07$; $P < 0.05$).

Discussion

We report that paroxetine is effective for both Panic Disorder (PD) and Panic Disorder with Agoraphobia (PGA). In our patient sample, the diagnosis of PDA was associated with more panic attacks per week than the diagnosis of PD alone. Our study shows that for both patients with PD and PDA, the relapse rate is the same whether the patient receives maintenance therapy for one or two years. Continuing paroxetine for an additional 12 months had no significant effect on relapse rates. This is one of the first studies to examine the effectiveness of long–term (up to 24 month) paroxetine therapy in preventing relapse in panic disorder.

The results of our study showed that paroxetine is highly efficacious in the short-term and intermediate-term treatment of PD and PDA, and this is consistent with the results of numerous efficacy studies [21-23]. The high efficacy rate of paroxetine pharmacotherapy also closely reflects the high response rates seen with Cognitive Behavioral Therapy [3]. Interestingly, our relapse rate of 15–18% after medication discontinuation parallels the 15% relapse rate reported by Park et al during a two year follow-up after 14 weeks of successful behavioral therapy for PD [24]. Our relapse rate of 15–18% during the one year discontinuation follow-up phase, however, is lower than reported in another medication discontinuation study. Mavissakalian et al in a small, prospective study examined PDA patients who received imipramine (IMI) for a second year of maintenance therapy and then were followed for 6 months after medication discontinuation

Table 3: Comparison of Panic Disorder versus Panic Disorder with Agoraphobia

	PD	PD and AGORAPHOBIA	df	X^2	p
	(N = 85)	(N = 58)			
	X ± SD	X ± SD			
Age	38.6 ± 1	40.0 ± 8			NS
Gender (F/M)	45/40	33/25			NS
Age group (≤50, >50)	73/12	50/8			NS
Relapse	14%	19%			NS
Weight gain	5.6 ± 3.3	5.4 ± 3.7			NS
Sexual dysfunction	19 (22%)	24 (41%)	1	5.93	0.015

[20]. The results of this study showed a relapse rate of up to 37%. Also, results of the IMI study showed that a second year of treatment was associated with improved outcome in terms of relapse prevention. We hypothesize that the differences in the study design may account for the lower relapse rate seen in our study. It is possible that paroxetine therapy is superior to IMI therapy in terms of relapse prevention. Alternatively, a selection effect may account for the relatively better outcome of our study patients after paroxetine discontinuation. Our patients did not have comorbid axis I disorders, and it is possible that the lack of comorbid diagnoses lowers the risk of relapse.

In our study, we were able to examine the side effects of paroxetine over a 24 month period. We observed that sexual side-effects were reported by 30% of the patients who received maintenance therapy. This finding is consistent with previous studies which demonstrated that up to 75% of the patients who receive paroxetine report sexual dysfunction [25-27].

We found that paroxetine pharmacotherapy produced a similar weight gain in both the 12 and 24 month maintenance therapy subgroups. From this finding, we postulate that weight gain related to paroxetine occurs mainly during the first 12 months of treatment. Interestingly, we observed that weight gain in both the intermediate and long-term treatment groups was positively correlated with risk of relapse. It is possible that a greater increase in body weight could lead to an increased risk of panic attacks because of psychobiological effects. Alternatively, the relatively small number of patients who relapsed could cause a β error therefore biasing our results. Further studies are needed in order to clarify this issue.

Patients who received adjunctive benzodiazepines during the initiation of paroxetine therapy had a greater tendency to relapse following 12 months of paroxetine maintenance treatment. We can assume that the use of adjunctive benzodiazapines early in treatment is related to a higher baseline anxiety level. This finding suggests, therefore, that a higher level of anxiety at the start of treatment is associated with a greater risk of future relapse. Further research is needed in order to examine the possibility that higher baseline anxiety levels may represent a risk factor for later relapse. It is possible that close psychiatric follow-up after termination of maintenance pharmacotherapy may be especially indicated for these patients. Patients treated with benzodiazepine augmentation therapy also showed a tendency to gain more weight. Further studies are needed in order to address the question of whether patients suffering from higher baseline anxiety levels may be at increased risk for weight gain with paroxetine treatment.

Our study results indicate that being agoraphobic potentiates the sexual side effects induced by paroxetine in patients with panic disorder. It is not clear why the agoraphobic patients tended to report more sexual side effects with paroxetine treatment. Perhaps for psychodynamic reasons, agoraphobic patients are more likely to suffer from sexual dysfunction and are therefore more sensitive to medication induced sexual side effects. Alternatively, we cannot rule out the possibility that our cohort of agoraphobic patients suffered from an increased level of sexual dysfunction at baseline and therefore selection bias may represent a confounding variable in our results. The higher level of anxiety seen in agoraphobic patients may predispose them to have an increased tendency for somatic complaints including higher rates of sexual dysfunction.

The primary strength of this preliminary study is that it is a real life outcome study whose longitudinal design closely reflects actual clinical practice. In addition, the rel-

atively large sample size and the high retention rate strengthen our results. The major limitations of our study include the use of non-blinded raters, the lack of a placebo control group, and the non-randomization of the two subsamples of patients treated for 12 and 24 months. Without the use of a placebo control group, we cannot rule out the possibility that the raters were unintentionally biased to see positive results (in both the maintenance and discontinuation phases) in all patients. A randomized, double-blind study is needed in order to confirm our findings.

Competing interests

None declared.

Authors' contributions

PND was the primary investigator; PND, II, AC performed the clincal investigation (diagnosis, treatment and follow up phases); KL drafted the manuscript and participated in the design; LG & MK participated the design and co-ordinated the study

All authors approved the final manuscript

Acknowledgements

The authors thank Mrs. Susan J Romano and Ms. Dana Polack for their technical assistance in this article.

References

1. Hirschfeld RM: **Panic Disorder: Diagnosis, epidemiology, and clinical course.** *J Clin Psychiatry* 1996, **57(Suppl 10):**3-8.
2. Salzman C: **Benzodiazepine treatment of panic and agaraphobic sympthoms: use, dependence, toxicity, abuse.** *J Psychiatric research* 1993, **27:**97-100.
3. Beck AT, Sokol L, Clark D, *et al.*: **A crossover study of focused cognitive therapy for panic disorder.** *Am J Psychiatry* 1992, **149(6):**778-783.
4. Davidson JR: **The use of benzodiazepines in panic disorder.** *J Clin Psychiatry* 1997, **58(Suppl 2):**26-8.
5. Davidson JR: **The long-term treatment of panic disorder.** *J Clin Psychiatry* 1998, **59 Suppl 8:**17-21.
6. Gunasekara NS, Noble S, Benfield P: **Paroxetine. An update of its pharmacology and therapeutic use in depression and a review of its use in other disorders.** *Drugs* 1998, **55(1):**85-120.
7. Jefferson JW: **Antidepressants in panic disorder.** *J Clin Psychiatry* 1997, **58(Suppl 2):**20-4.
8. Rosenberg NK, Andersch S, Kullingsjo H, *et al.*: **Efficacy and safety of Alprazolam, Impramine and placebo in treatment of panic disorder.** *Acta Psychiatrica Scandinavica* 1991, **Supple 365:**18-27.
9. Medign K, Westberg P, Eriksson E: **Superiority of Clomipramine over imipramine in the treatment of panic disorder: A placebo-controlled trial.** *J Clin Psychopharmacol* 1992, **12:**251-261.
10. Wada AG: **Antidepressants in Panic Disorder.** *Int Clin Psychopharmacol* 1999, **14(supple 2):**S13-7.
11. American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Panic Disorder.** *Am J Psychiatry* 1998, **155(May suppl):**1-34.
12. Bakkar A, van Balkom AJ, Spinhoven P: **SSRIs vs. TCAs in the treatment of panic disorder: a meta-analysis.** *Acta Psychiatr Scand* 2002, **106(3):**163-7.
13. Boyer W: **Serotonin uptake inhibitors are superior to imipramine and alprazolam in alleviating panic attacks; A meta-analasis.** *Int Clin Psychopharmacol* 1995, **10:**45-49.
14. De Boer JA, Westenberg HGM, Kamerbeek WD, *et al.*: **Effects of serotonin uptake inhibitors in anxiety disorders: A double blind comparison of clomipramine and fluvoxamine.** *Int Clin psychopharmacol* 1987, **2:**21-32.
15. Lydiard RB, Steiner M, Burnham D, Gergel I: **Efficacy Studies of Paroxetine in Panic Disorder.** *Psychopharmacology Bulletin* 1998, **34(2):**175-182.
16. Lecrubier Y, Bakker A, Dunber G, *et al.*: **A comparison of paroxetine, clompiramine and placebo in the treatment of panic disorder.** *Acta Psychiatr Scand* 1997, **95:**145-52.
17. Oehrberg S, Christiansen PE, Behnke K, *et al.*: **Paroxetine in the treatment of panic disorder a randomised, double blind, placebo controlled study.** *Br J Psychiatry* 1995, **167:**374-9.
18. Modell JG, Katholi CR, Modell JD, DePalma RL: **Pharmacoepidemiology and Drug Utilization. Comparative sexual side effects of burpropion, fluoxetine, paroxetine, and sertraline.** *Clin Pharmacol Ther* 1997, **61(4):**476-487.
19. Michelson D, Lydiard RB, Pollack MH, *et al.*: **Outcome assessment and clinical improvement in panic disorder: evidence from a randomized controlled trial of fluoxetine and placebo. The fluoxetine panic disorder study group.** *Am J Psychiatry* 1998, **155:**1570-1577.
20. Mavissakalian MR, Perel JM: **2nd year maintenance and discontinuation of imipramine in PD with agoraphobia.** *Ann Clin Psychiatry* 2001, **13:**63-67.
21. Bakkar A, Van-Dyck R, Spinhoven P, Van-Balcom AJ: **Paroxetine, clomipramine, and cognitive therapy in the treatment of panic disorder.** *J Clin Psychiatry* 1999, **60(12):**831-8.
22. Ballenger GC, Wheadon DE, Steiner M, *et al.*: **Double-blind, fixed-dose placebo-controlled study of paroxetine in the treatment of panic disorder.** *Am J Psychiatry* 1998, **155(1):**36-42.
23. Judge R, Burnham D, Steiner M, *et al.*: **Paroxetine long-term safety and efficacy in panic disorder and prevention of relapse: a double-blind study.** *Eur Neuropsychopharmacol* 1996, **6(Suppl 1):**26.
24. Park JM, Mataix-Cols D, Marks IM, *et al.*: **Two–year Follow-up after a randomized controlled trial of self and clinician accompanied exposure for phobia/panic disorders.** *Br J Psychiatry* 2001, **178:**543-548.
25. Kennedy SH, Eisfeld BS, Dickens SE, Bacchiochi JR, Bagby RM: **Antideperessant induced sexual dysfunction during treatment with moclobemide, paroxetine, sertraline, and venlafaxine.** *Journal Clin Psychiatry* 2000, **61(4):**276-281.
26. Lecrubier Y, Judge R: **Collaborative paroxetine Panic Study Investigators. Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder.** *Acta Psychiatr Scand* 1997, **95:**153-60.
27. Zajecka J, Mitchell S, Fawcett J: **Treatment-emergent changes in sexual function with selective serotonin reuptake inhibitors as measured with the Rush sexual inventory.** *Psychopharmacol Bull* 1997, **33(4):**755-60.

Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-244X/4/16/prepub