Pharmacotherapy of panic disorder in the elderly: a naturalistic 12-month follow-up outcome study

Pinhas N Dannon†, Iulian Iancu, Katherine Lowengrub, Leon Grunhaus & Moshe Kotler

†Author for correspondence
The Rehovot Community Mental Health & Rehabilitation Clinic, Remez Street 80, 76449, Rehovot, Israel
Tel.: +97 289 461 893
Fax: +97 289 468 962
pinhasd@post.tau.ac.il

Background: Despite the previously accepted notion that panic disorder (PD) is rare in the elderly, recent data have shown that late-life PD may be more common than previously thought. Paroxetine is a selective serotonergic reuptake inhibitor which has had clear efficacy in the treatment of PD in the general adult population. In this study we aimed to examine the treatment outcome of paroxetine pharmacotherapy for late-life PD.
Method: In this long-term naturalistic follow-up study, a group of 61 elderly (aged 59 years or older) PD patients were compared with a group of 95 younger (aged between 18 and 59 years) PD patients in terms of treatment response to paroxetine pharmacotherapy. The two groups were followed during both the initial short-term treatment phase (first 3 months) and throughout long-term (month 4–12) maintenance treatment. The two groups were also compared for side effects of paroxetine therapy.
Results: No differences were found between the two patient groups in terms of response rate, side effects and tolerability of drug treatment. **Conclusions**: The use of paroxetine for the treatment of late-life PD appears to be both beneficial and well tolerated. Further controlled studies are needed to confirm these preliminary results.

Keywords: elderly, panic disorder, paroxetine, SSRI, treatment outcome

Panic disorder (PD) is one of the most common anxiety disorders and has a lifetime prevalence of 3 to 5% [1]. PD is characterized by recurrent, unexpected panic attacks followed by a persistent concern about having additional attacks [2]. The panic attack itself is defined as a discrete period of intense fear accompanied by the abrupt development of a range of autonomic symptoms, which may include dizziness, chest pain, palpitations, sweating, shortness of breath, nausea and paresthesias. Typically, the autonomic symptoms are accompanied by cognitive symptoms such as a fear of dying or losing control or 'going crazy.' Anxiety about having the next attack is often associated with the development of avoidant behavior. The affected individuals may avoid any situation in which they perceive that they would be embarrassed or that help may not be available in the event that a spontaneous panic attack should occur. These individuals may avoid family and social gatherings, public places or traveling. The avoidant behavior can lead to a significant decline in social functioning, which may, in turn, contribute to feelings of loneliness and isolation. Furthermore, individuals with PD are frequent users of both emergency and general medical treatment. Therefore, this disorder has significant costs for the healthcare delivery system [3].

PD in the elderly represents an especially challenging clinical diagnosis because this population suffers from a relatively high rate of chronic physical disorders including cardiovascular, pulmonary and gastrointestinal disease. The evaluation of panic symptoms in the elderly patient must include a careful history and physical examination, as well as routine laboratory tests to rule out an organic cause [4,5]. For example, in the elderly, side effects of medication and/or psychoactive substances such as caffeine and nicotine may precipitate or provoke anxiety symptoms. Some individuals with PD are convinced that the attacks are indicative of serious medical illness and seek out repeated medical consultation in order to allay their fears. The correct diagnosis and treatment of PD therefore, allows the patient to avoid unnecessary medical tests and leads to an improvement in the quality of life.

While the elderly PD patient may suffer from a chronic and relapsing form of the disorder, which started in young adulthood, PD is also known to present with an onset in late life. Data from the Longitudinal Aging Study Amsterdam (LASA) suggest that the 6-month prevalence rate of PD in the elderly is around 1% [6] which is comparable with a 1.4% 12-month prevalence rate reported in the National Comorbidity Study (NCA) and the Epidemiological Catchment

Area survey (ECA) [7]. Lenze and colleagues found that in adults with a primary depressive disorder, the prevalence of comorbid PD was 9.3% [8].

With the exception of one open-label trial [9], there have been no randomized controlled trials on the pharmacologic treatment of late-life PD, and recommendations for the management of PD in the elderly have been extrapolated from research based on younger patients [10]. According to the current APA practice guidelines, selective serotonin reuptake inhibitor (SSRIs) should be considered as first-line agents in the treatment of PD since these agents have the most favorable balance of efficacy and side effects [11]. The APA recommends that pharmacotherapy for PD should continue for at least a year, and the combination of SSRI pharmacotherapy and cognitive behavior therapy (CBT) appears to give the best overall treatment response [11].

Current recommendations for the management of PD include that benzodiazepines be used only for the rapid stabilization of symptoms at the beginning of treatment [12–14]. Benzodiazepines should be coadministered with the SSRI at the onset of treatment and then tapered and discontinued after 6 to 8 weeks. Studies have shown that despite these guidelines, PD patients are maintained on chronic doses of benzodiazepines, thus exposing the patients to the risk of dependency [15]. Prolonged benzodiazepine use may be especially hazardous in the elderly being associated with an increased risk of cognitive impairment, falls and fractures [16].

Paroxetine was the first SSRI approved for the treatment of PD and its efficacy and tolerability have been demonstrated in multiple open-label and randomized double-blind trials [11,17,18]. Clinical trials of paroxetine in the treatment of late-life depression have shown the drug to be well tolerated with a favorable side-effect profile in the elderly [19,20]. The purpose of this study was to examine the outcome of long-term (up to a year) paroxetine pharmacotherapy in the treatment of late-life PD by comparing treatment responses in the elderly group versus a younger cohort.

Sample

156 PD/PD with agoraphobia (PDA) patients were included in our study. The whole sample consisted of 87 females, and 69 males. All subjects met the DSM-IV diagnosis of PD (n = 103) or PDA (n = 53). Patients were in good general medical health. In total, 34 patients had stable medical conditions such as mild ischemic heart disease (n = 14), mild hypertension (n = 12), non-insulin dependent diabetes mellitus (n = 6), hypothyroidism (n = 3), benign prostatic hypertrophy (n = 3) and cataracts (n = 2).

Study design

The study was conducted at the Sheba Medical Center, a tertiary medical center in Israel. The participants were referred to the hospital outpatient psychiatry clinic by an emergency room physician/psychiatrist or by their general practitioners. All patients underwent a comprehensive, psychiatric semi-structured diagnostic evaluation performed by a senior psychiatrist (PND II). Inclusion criteria were a diagnosis of PD or PDA according to DSM-IV diagnostic criteria. Exclusion criteria were

- Age less than 18
- Comorbid axis I diagnosis including schizophrenia, bipolar disorder, and substance abuse (alcohol and illegal drugs)
- Previous treatment with paroxetine
- Unstable medical disease
- Dementia

We note that patients with a diagnosis of comorbid major depression were not excluded if the depression started after the onset of panic symptoms. All patients gave their informed consent for participating in the study at the time of enrollment. The study was approved by the hospital's Helsinki Committee and the Ministry of Health.

This age allocation is similar to that used by van Hout, who defined the older population as between 55–85 years [21]. No statistical differences were noted between our younger and older groups regarding baseline ratings.

- Younger group (age 18–59 years, n = 95)
- Older group (age > 59 years, n = 61)

Patients in both groups received psychopharmacologic treatment with paroxetine according to the same titration schedule. Paroxetine was commenced at a dose of 5 mg/day – a quarter of a 20 mg tablet – on days 1 and 2, and then increased to 10 mg/day on days 3 to 7. On day 8 of treatment, paroxetine was increased to 20 mg/day and maintained at this dose until the end of the fourth week of treatment. At the end of week 4, patients who had a good treatment response, that is, a significant decrease in the rate of panic attacks, were maintained at 20 mg/day, while the remaining patients were increased to a dose of 40 mg/day. At week 12 of the study, all patients who had a good treatment response were maintained on paroxetine

and continued in the 12-month follow-up phase. Treatment response was defined as zero panic attacks during the preceding 1-week period. The average daily dose used for the young cohort during months 3 to 12 was 32.5 + 7.6 mg/day compared with an average daily dose of 28.3 + 9.4 mg/day in the old cohort.

It should also be noted that adjunctive benzodiazepine therapy with lorazepam was permitted during the first 3 months of our study. In both age groups, lorazepam was started (on day 1 of the study) in a subset of patients at a dose of 0.5 mg 2 to 4-times/day – total dose of 1 to 2 mg/day – according to severity of panic symptoms. Lorazepam was then continued until the end of week 8 of the study, at which time a gradual taper schedule was begun; the total daily dose of lorazepam was reduced by 25% every 4 days, and lorazepam was discontinued completely by week 12 of the study.

Instruments

An experienced rater administered several questionnaires rating anxiety, depression and functioning. The instruments were administered at baseline and then monthly up to the 12-month visit. We administered the Hamilton Rating Scale for Anxiety (HAM-A) [22], the Hamilton Rating Depression Scale-17 items (HRSD) [23], and the Panic Self Questionnaire (PSQ) [24].

Analysis

Statistical analyses were performed with t-test analysis, chi squares and ANalysis Of VAriance (ANOVA) with repeated measures. Repeated measures analysis of variance was performed on the rating scales scores in order to determine the presence of any group effect on anxiety and panic symptoms. The level of significance was set at 0.05, unless otherwise stated.

Results

Comparisons of elderly versus younger groups and results with two-tailed t-tests and ANOVA with repeated measures are displayed in **Table 1**. Patients in both the young and elderly groups demonstrated a good response to short- and long-term paroxetine treatment. At the 12-week visit, 77% of patients in the younger group and 74% in the elderly were full responders. At the 12-month visit, 82% of the young patients and 79% of the elderly were full responders. Full response at both the 3- and 12-month end points was defined as the absence of panic attacks in the previous week. In both age groups a reduction in the PSQ and the HAM-A was seen at the 12-week visit as compared with baseline and this improvement was maintained at the 12-month visit.

We report that the short- and long-term response to paroxetine was not different between the two patient groups. When we compared the mean results of the PSQ at the 3-month visit between the elderly (1.7 ± 0.9) and young (1.6 ± 0.8), there was no significant difference between the two groups (p = NS). Mean results of the HAM-A at the 3-month visit were not significantly different between the elderly (11.8 ± 4.7) and young (12.1 ± 5.2) groups. At the 12 month visit there were no significant differences between the elderly and younger patients as measured by the PSQ (1.3 ± 0.8, elderly versus 1.2 ± 0.9, young; p = NS) and the HAM-A (7.4 ± 4.3, elderly versus 8.8 ± 3.9, young; p = NS). We note that the HRSD at baseline was comparable in both groups (9.0 ± 2.8, elderly versus 10.1 ± 4.3, young; p = NS), and the HRDS showed a modest decline in both groups at the 3- (8.3 ± 2.0, elderly versus 8.6 ± 2.5, young; p = NS) and 12-month (6.0 ± 0.8, elderly versus 6.1 ± 1.2, young; p = NS) endpoints, with no significant differences between the elderly and young groups.

The overall response rate was similar in PD versus PDA patients (f = 0.38, df = 1:156, p = 0.85–NS). The number of patients who were treated with adjunctive lorivan in the elderly (31%) versus the younger group (29%) was not significantly different (t = 0.48, p = 0.44–NS).

The tolerability of paroxetine was similar across the study groups. Of the patients who experienced side effects, 35% were from the young and 38% from the elderly groups. The mean weight gain (as measured at the 12-month visit) in the elderly patients was 12.3 + 8.2 kg versus a mean weight gain of 11.1 + 10.2 kg in the younger patients (t = -0.78, p = 0.44–NS). The frequency of sexual side effects was similar among the young and elderly patients, respectively (t = -0.72, p = 0.47–NS). The frequency of other miscellaneous side effects was also comparable between the two groups (t = -0.48, p = 0.64–NS). The gender distribution was similar between the two groups, and gender had no significant effect on response rate (f = 3.06, df = 1:156, p = 0.8–NS).

Expert opinion

This is one of the first studies, to our knowledge, to examine the use of paroxetine in the treatment of late-life PD. While the tolerability and efficacy of SSRIs for the treatment of PD in adults is well documented, the treatment of late-life PD has not

Table 1. Comparison between elderly and younger patients at baseline and at the 3 and 12-month visits.

	Elderly patients 59 < n = 61	Younger patients 18–59, n = 95	p-value
Number of patients (female/male)	36/25	51/44	
Diagnosis PD/PDA	40/21	63/32	NS
PSQ – baseline	5.3 ± 2.3	5.8 ± 0.9	NS
HAM-A – baseline	19.7 ± 3.8	18.3 ± 4.6	NS
HRSD – baseline	9.0 ± 2.8	10.1 ± 4.3	NS
PSQ – 3 months	1.7 ± 0.9	1.6 ± 0.8	NS
HAM-A – 3 months	11.8 ± 4.7	12.1 ± 5.2	NS
HRSD – 3 months	8.3 ± 2.0	8.6 ± 2.5	NS
PSQ – 12 months	1.3 ± 0.8	1.2 ± 0.9	NS
HAM-A – 12 months	7.4 ± 4.3	8.1 ± 3.9	NS
HRSD – 12 months	6.0 ± 0.8	6.1 ± 1.2	NS

HAM-A: Hamilton Rating Scale for Anxiety; HRSD: Hamilton Rating Scale for Depression; NS: Not significant; PD: Panic disorder; PSQ: Panic Self-Questionnaire.

been well studied. In this study, we compared the use of paroxetine for the treatment of PD in young to middle-aged adults (aged 18–59 years) versus the elderly (>59 years of age). This 12-month outcome study followed both groups in the acute treatment phase (first 3 months) and in the long-term maintenance phase (4–12 months) of PD. The results of our study demonstrate that paroxetine was beneficial in elderly PD patients, and the response rate seen in our elderly patients was comparable to the response rate seen in our younger sample.

Our study also shows that paroxetine was well tolerated in our elderly sample. The side-effect profile seen in the elderly patients was comparable with that in their younger counterparts, and no serious adverse events were observed. Common side effects observed in both groups at the beginning of treatment included nausea, dizziness, fatigue and headache, which occurred at similar rates in both groups. Side effects seen with long-term treatment included weight gain and sexual dysfunction and were observed at comparable rates in both groups.

The results of our study are consistent with the existing literature on late-life depression, which shows SSRIs to be well tolerated overall in the elderly [11,25]. The obvious advantages of SSRIs compared with tricyclic antidepressants in the elderly include fewer anticholinergic effects, a benign cardiovascular profile, ease of use and safety in overdose. However, according to Herrmann, the elderly may be more susceptible to the less common, underappreciated risks of SSRIs, including hyponatremia, falls and weight loss [26]. Spigset, in a study investigating the pattern of adverse reactions reported with the use of SSRIs in Sweden, demonstrated that parkinsonism, confusion, hallucinations, euphoria, hyponatremia and bradycardia were reported more often in the elderly [27]. Note that hyponatremia was found to be more common in women and was observed in patients with above-average SSRI dosages. The above severe side effects of paroxetine were not seen in our sample of elderly patients, and this was most likely to be due to the relatively low rate of these events. Furthermore, our patients were generally in good health and so may have been less vulnerable to serious side effects. A consideration of the safety profile of paroxetine must include a discussion of the potential for drug–drug interactions. A number of important pharmacokinetic and pharmacodynamic drug interactions are observed with paroxetine. All SSRIs could potentially cause fatal hypermetabolic syndrome when administered together with a monoamine oxidase inhibitor. Paroxetine inhibits the P4502d6 isoenzyme, causing elevated levels of any coadministered drug also metabolized by this enzyme. In addition, paroxetine is highly bound to plasma proteins and can displace other drugs such as carbamazepine, phenytoin and warfarin from their protein binding sites [28].

Pharmacokinetics in the elderly have been studied on a range of SSRI agents. The half-life of fluoxetine does not appear to be significantly different in the elderly [29], and no pharmacokinetic differences were seen with fluvoxamine in this age group. A study of younger (aged 18–45 years) and older (>65 years) volunteers showed a similar

Executive Summary

- This is one of the first studies to examine the use of serotonin reuptake inhibitors (SSRIs) in the treatment of late-life panic disorder (PD).
- The results of our study demonstrate that paroxetine was beneficial and well tolerated in elderly PD patients.
- No significant differences were noted between our older and younger cohorts of PD patients in terms of response rate, side effects and tolerability of treatment.

sertraline half-life in all groups [30]. A study of paroxetine showed that blood levels with 20 mg/day in the elderly can be similar to those of 30 mg/day in younger adults, and lower initial doses of paroxetine are recommended for the elderly [31]. While the above studies may provide a guide to dosing strategies, it must be emphasized that there is wide variation in the pharmacokinetics of paroxetine in adults as well as in the elderly, and therefore the optimal therapeutic dose may vary greatly, especially in the elderly [32]. Our sample of elderly patients tolerated a standard adult dose of paroxetine of 20 to 40 mg/day.

The primary strength of this 1-year naturalistic outcome study is the long-term study design. We were able to demonstrate that paroxetine was beneficial and well tolerated in our elderly PD cohort not only in the short-term phase but also in the long-term maintenance phase. The major limitation of this study is the lack of a placebo control group, for a randomized, controlled study design is necessary in order to demonstrate the efficacy of paroxetine in the treatment of late-life PD. Another limitation of the study is the exclusion of patients with severe medical conditions. Given that elderly PD patients may commonly suffer from significant physical disease, and it would be important to demonstrate the tolerability and efficacy of paroxetine in a cohort of patients, which reflects actual clinical practice.

We recommend that further studies are warranted to confirm our preliminary findings about the long-term efficacy, tolerability and safety of paroxetine in the treatment of late-life PD. Furthermore, we hope that this study will be part of a trend toward increased focus on the relatively new field of late-life anxiety disorders.

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Affiliations

Pinhas N Dannon, MD
The Rehovot Community Mental Health & Rehabilitation Clinic, Remez Street 80, 76449, Rehovot, Israel
Affiliated with the Saekler School of Medicine, Tel Aviv, Israel
Tel.: +97 289 461 893
Fax: +97 289 468 962
pinhasd@post.tau.ac.il

Iulian Iancu, MD
The Beer Yaakov Hospital, Beer Yaakov, Israel

Katherine Lowengrub, MD
The Rehovot Community Mental Health & Rehabilitation Clinic, Remez Street 80, 76449, Rehovot, Israel

Leon Grunhaus, MD
Tel Aviv University, The Psychiatry Ward C, Chaim Sheba Medical Center, Affiliated with the Sackler School of Medicine, Tel Aviv, Israel

Moshe Kotler, MD
The Beer Yaakov Hospital, Beer Yaakov, Israel