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Chronology of Panic and Avoidance, Age of Onset in Panic Disorder, and Prediction of Treatment Response

A Report from the Cross-National Collaborative Panic Study

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Summary. The relevance of the chronology between panic disorder and avoidance behavior and of an early, medium or late onset of panic disorder was tested. Groups from the sample of the cross-national collaborative panic study (CNCPS) were compared for differences in basic characteristics and for the ability to predict treatment response. Patients who developed avoidance behavior before the full syndrome of panic disorder had less often a full agoraphobia but were not different in their response to treatment. Patients with an early onset of panic disorder suffered more often from agoraphobia. The treatment response was similar in the groups with early, medium or late onset of panic disorder. Neither the chronology between panic disorder and avoidance behavior nor the age of onset of panic disorder predicted outcome in short-term treatment with alprazolam or imipramine.

Key words: Panic disorder – Age of onset – Avoidance behavior – Agoraphobia – Treatment response – Imipramine – Alprazolam

Introduction

In the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) (APA 1987) panic and agoraphobia are presently conceptualized as a clinical entity. Following the model of Klein (Klein et al. 1987), panic attacks are seen as the central feature whereas avoidance behavior is a secondary complication, which may develop in a subgroup of patients. In clinical samples most cases with agoraphobia report that they have experienced panic attacks, but there is group that suffers from avoidance behavior before a fully diagnosable panic disorder is present. To our knowledge, no information is available whether patients who develop avoidance behavior before or at the same time with the onset of panic disorder differ in severity and treatment response from those that follow the "classic" pattern, in which case panic disorder is manifested before the onset of agoraphobia.

Furthermore, little is known about differences in clinical features and treatment response between subjects with early or late onset of panic disorder. In a majority of patients in epidemiological (Wittchen 1986) and clinical samples (Breier et al. 1984; Buller et al. 1986; Thyer et al. 1985) panic disorder has its onset between the ages of 20 to 30 years. The DSM-III-R (APA 1987) states that the onset of panic disorder is in the late 20s and that panic disorder with agoraphobia is uncommon before age 18. However, based on data from the Epidemiological Catchment Area Program, von Korff and co-workers (1985) reported an even earlier age of onset, with a peak at 15–19 years. In a study on ninth-grade students, the lifetime prevalence rate for panic attacks (but not panic disorder) was as high as 11.6% (Hayward et al. 1989). Recently, Moreau et al. (1989) reported on children at high risk for depression, in whom the age of onset of panic attacks ranged from 5–18 years. Although other forms of anxiety like school phobia, overanxious disorder or separation anxiety disorder are more prominent in childhood and adolescence (Kashani and Orvaschel 1988) some of these may function as risk factors or precursors (Weissman 1985) for adult forms of anxiety like agoraphobia (Zitrin and Ross 1988). At the other end of the scale, researchers have raised doubts as to whether a diagnosis of panic disorder is appropriate in patients who develop the symptoms after age 40. Marks and Lader (1973) argue that "anxiety which begins for the first time after the age of 40 is commonly part of a depressive syndrome rather than of an anxiety state." This position is also held in the diagnostic criteria developed by Feighner et al. (1972), which exclude patients from a diagnosis

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of anxiety neurosis when the age of onset is later than age 40. However, Luchins and Rose (1989) recently described three patients with an age of onset of panic disorder between 75 and 87 years.

On the basis of data from the Cross-National Collaborative Panic Study, which compared the efficacy of alprazolam and imipramine with that of placebo in panic disorder during an 8 week trial (Cross-National Collaborative Panic Study Second Phase Investigators 1989), we were able to approach the following questions:

1. Does the chronology of panic and avoidance behavior (panic first, avoidance first, contemporaneous onset, or no avoidance) lead to differences with respect to (a) baseline severity and (b) response to short-term drug treatment?

2. Is the age of onset in panic disorder (early, medium, or late onset) associated with differences in (a) baseline characteristics or (b) short-term treatment response?

Methods

Subjects. The number of patients entered into the study was 1168. Subjects were recruited in 12 centers (i.e. randomization blocks) in 14 countries. Most patients were female (62%). Subjects younger than 18 or older than 65 were excluded. The mean age at the time of the study was 34 years, the mean age of onset of panic disorder was 29 years, the mean age of onset of avoidance behavior was 28.4 years in patients with avoidance behavior. All patients received a diagnosis of panic disorder but showed different degrees of avoidance behavior (none, limited, extensive). Subjects were experiencing at least one panic attack per week for the last 3 weeks before the study. The diagnostic evaluation was based on a standardized interview, the Structured Clinical Interview for DSM-III Upjohn Version (SCID-UP) developed by Spitzer and Williams (1983). "Limited phobic avoidance" was defined in the SCID-UP as "significant phobic avoidance or endurance with dread, but less than agoraphobia," "extensive phobic avoidance" was defined as "generalized travel restrictions, often needs a companion away from home, or markedly altered life-style." Information on age of onset of panic disorder and of avoidance behavior was also gathered during the SCID interview. The age of onset was defined as that age when the patient met criteria for a diagnosis of panic disorder for the first time. The test-retest reliability for age of onset of panic disorder using interview data has been excellent (Prusoff et al. 1988).

Any psychotropic medication was stopped at least 1 week before baseline when the study medication began with one capsule per day (1 mg alprazolam or 25 mg imipramine). The dose could be increased by one capsule every 3 days up to a maximum daily dose of ten capsules until an adequate clinical effect was seen. The average daily dose at the end of the trial was 5.7 capsules (5.7 mg) for alprazolam, 6.2 capsules (155 mg) for imipramine and 6.8 capsules for placebo. Further details about the study design and outcome data are given elsewhere (Cross-National Collaborative Panic Study Second Phase Investigators 1989).

Group Formation. To address the question of the relevance of chronology of panic disorder and avoidance behavior the sample was subdivided into four groups: (1) no avoidance behavior ($n = 257$, 22.5%), (2) contemporaneous onset (in the same year) of panic and avoidance behavior ($n = 492$, 43.1%), (3) panic disorder first ($n = 216$, 18.9%), (4) avoidance behavior first ($n = 177$, 15.5%).

In a second step, the same sample was subdivided into three groups with an early, medium or late onset of panic disorder. In patients with "early onset" ($n = 218$, 18.7%) the disorder started before age 20 years. Subjects with an onset between 20 and 29 ($n = 442$, 37.8%) were allocated to the "medium onset" group, and those with an onset after the age of 30 ($n = 508$, 43.5%) to the "late onset" group.

Assessments of Severity and Outcome. Outcome data were collected at weekly visits. Measures for severity and assessment of treatment response used in this report include:

(1) The number of spontaneous panic attacks per week, rated on the Panic Attack Scale developed by Sheehan (1984) for which the information was collected in the patient's weekly diary;
(2) Anticipatory anxiety during a particular week, which was measured by the percentage of time in which the patient worried about having a panic attack;
(3) A weekly global phobia score which described the overall distress associated with phobic symptoms on a 11-point scale (0–10) derived from the scale developed by Marks and Mathews (1979):
(4) Work and social disability (social functioning) assessed on a five point scale (1–5);
(5) Severity of anxiety measured on the 14-item Hamilton anxiety scale (Hamilton 1959);
(6) Severity of depression measured on the 21-item Hamilton Depression Scale (Hamilton 1960)
(7) Global improvement rated by the patient and the physician on a 11-point scale (0–10). The midpoint (5) means "unchanged" and is the baseline against which either improvement (score of 6–10) or worsening (score of four to zero) is measured. Baseline and endpoint (week-8) values are reported in this paper.

Statistical Analyses. The statistical analyses reported in this paper were conducted at the Biostatistics Unit, Massachusetts General Hospital, under the direct supervision of Philip W. Lavori, Ph.D. using the SAS program package (SAS 1982).

Comparison for sex ratio, degree of avoidance behavior, allocation to study medication and center effects was made by Chi-square statistics for the comparison groups defined by chronology of panic and avoidance and by age of onset of panic disorder.

Analyses of variance (ANOVA) were calculated for the baseline severity and outcome variables by way of the SAS general linear models procedure GLM. Each ANOVA for the baseline measures (dependent variable) was calculated in a three-way layout with the following independent variables: 12 centers (randomization blocks) by three degrees of avoidance behavior (panic disorder uncomplicated, with limited avoidance, with extensive avoidance) by the four (three) comparison groups. The main effects and all two- and three-way interactions were tested for significance in a hierarchical (GLM type 1 analyses) and a non-hierarchical manner (GLM type III analyses) (Fleiss 1986). For the type I analyses the factors were ordered in the hierarchy of how they affect the dependent variable (center, degree of avoidance behavior, comparison group). Before calculating the ANOVA for "number of spontaneous panic attacks" the variable was log-corrected because the counts were non-normally distributed.

Analyses for outcome (treatment response) were calculated only for patients who completed at least 3 weeks of therapy. ANOVAs were calculated separately for week 8 (completer analyses) and for the last week that the patient remained in the trial (endpoint analyses). Each ANOVA was calculated in a five-way layout with the following independent variables: baseline value of the dependent variable (dichotomized), center, degree of avoidance behavior, onset group, and medication (alprazolam, imipramine, placebo). Main effects, all two-way interactions and one three-way interaction (center by degree of avoidance behavior by "comparison group") were tested for significance by way of type I and type III analyses.

Results

Relevance of Chronology Between Panic and Avoidance

Sex ratio was significantly different between the four comparison groups, but this was only due to the low pro-

Table 1. Basic characteristics of comparison groups defined by temporal relation between onset of panic and onset of avoidance behavior

	No avoidance		Contemporaneous onset		Panic first		Avoidance first		
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	
Sex									
Male	123	(48.4)	171	(35.4)	73	(34.3)	57	(32.9)	$\chi^2 = 16.2$
Female	131	(51.6)	312	(64.6)	140	(65.7)	116	(67.1)	$df = 3, P = 0.001$
Subtype									
Panic disorder uncomplicated	257	(100.0)	–		–		–		
Panic disorder with limited avoidance	–		250	(50.8)	94	(43.5)	122	(68.9)	
Panic disorder with agoraphobia	–		242	(49.2)	122	(56.5)	55	(31.1)	
Medication									
Alprazolam	89	(34.6)	158	(32.1)	63	(29.2)	69	(39.0)	$\chi^2 = 6.8$
Imipramine	83	(32.2)	159	(32.3)	78	(36.1)	60	(33.9)	$df = 6$, n.s.
Placebo	85	(33.1)	175	(35.6)	75	(34.7)	48	(27.1)	

portion of female patients in the group with no avoidance (Chi-square = 16.2, $df = 3$, $P < 0.001$) (see Table 1). Testing for any association between chronology of avoidance (contemporaneous onset, panic first, avoidance first) and the degree of avoidance behavior (limited vs extensive phobic avoidance) revealed significant differences between the groups (Chi-square = 26.7, $df = 2$, $P < 0.0001$): the proportion with limited phobic avoidance was highest in the group with avoidance first and lowest in the group with panic first. Distribution across the three treatment modalities was similar for the four comparison groups (Chi-square = 6.8, $df = 6$, n.s.).

There was a significant difference (center effect) for the frequency distribution between the comparison groups in different sites (Chi-square 167.0, $df = 33$, $P < 0.0001$). Patients with "no avoidance" were most often seen in Brazil (41.4% of their sample) and least often in Canada (7.6%). However, Canada showed the highest rate (53.3%) for "contemporaneous onset," whereas the lowest rate for this group was seen in Mexico (19.7%). This center also had the highest percentage of patients with "avoidance first" (43.6%), while the lowest rate of avoidance first was seen in Italy (27.0%). For "panic first" the highest rate was seen in Germany-Austria (31.1%), and the lowest in Belgium (6.1%).

Means and standard deviations of baseline severity measures are given in Table 2. Tests of significance refer to the main effect of the grouping variable (chronology between onset of panic disorder and onset of avoidance behavior) after controlling for center effects and degree of avoidance behavior (hierarchical order in GLM type 1 analyses) because these variables had a significant effect on severity (Cross-National Collaborative Panic Study Second Phase Investigators 1989). At baseline the number of spontaneous panic attacks was similar in the four groups. Although the group with no avoidance showed the lowest scores on measures of anticipatory anxiety, global phobia, work and social disability and on both Hamilton scales (Anxiety, Depression), there were no statistically significant group differences (see Table 2).

Table 2 also gives the results for the outcome at endpoint. Overall, the group without avoidance behavior had the best outcome. But controlling for baseline severity, center effects, degree of avoidance behavior and medication disclosed no statistically significant effect of the grouping variable on treatment response (GLM type 1 analyses). Except for the variable "patient-rated improvement," which showed a statistically significant group difference, the same results were seen in the completer analyses (week-8 comparison), which are therefore not given in a separate table.

Relevance of Age of Onset of Panic Disorder

In the groups with early, medium or late onset the sex ratio was similar, showing a preponderance of female patients. Allocation to treatment modality did not differ between the groups. However, there was a significant association between the degree of avoidance behavior and an earlier onset: the group with early onset had the highest rate of panic disorder with extensive avoidance (47%) (see Table 3).

For frequency distribution of onset groups in different sites there was a significant center effect (Chi-square 60.554, $df = 22$, $P < 0.0001$). The highest percentage of early onset cases was seen in Canada (28.6%), and the lowest rate for this group in Colombia (10.3%). This center also had the highest percentage of late onset cases (58.9%), while the lowest rate of late onset panic disorder was seen in Italy (27.0%).

Baseline severity measures (means and standard deviations) are given in Table 4. Tests of significance refer to the main effect of the grouping variable (onset of panic disorder) after controlling for center effects and degree of avoidance behavior (hierarchical order in GLM type 1 analyses). Groups did not differ with respect to severity of the disorder at baseline (see Table 4), with one exception: the late onset group different from the medium onset group at the 5% significance level, with a higher depression rating on the Hamilton Depression Scale. Taking into consideration a need for adjustment for multiple testing, this finding may still have been caused by chance.

Table 2. Baseline and outcome characteristics in comparison groups defined by temporal relation between onset of panic disorder and onset of avoidance behavior

	Baseline [Mean (SD)]				Endpoint [Mean (SD)]			
	No avoidance	Contemporaneous	Panic first	Avoidance first	No avoidance	Contemporaneous onset	Panic first	Avoidance first
No. of spontaneous panic attacks (log)	1.35 (1.33) $n = 256$	1.04 (1.48) $n = 487$	1.14 (1.49) $n = 216$	1.26 (1.60) $n = 175$	−0.37 (1.27) $n = 223$	−0.36 (1.28) $n = 429$	−0.36 (1.36) $n = 185$	−0.33 (1.34) $n = 154$
Anticipatory anxiety (% of time)	38.17 (32.07) $n = 254$	45.37 (32.56) $n = 486$	44.85 (31.90) $n = 216$	39.58 (32.68) $n = 175$	13.27 (22.62) $n = 223$	18.98 (25.59) $n = 426$	18.64 (25.45) $n = 185$	16.40 (22.83) $n = 154$
Global phobia score (1–10)	3.25 (2.98) $n = 254$	6.89 (2.26) $n = 486$	6.98 (2.32) $n = 216$	6.94 (2.23) $n = 174$	1.81 (2.36) $n = 223$	3.67 (2.82) $n = 425$	3.91 (2.85) $n = 185$	3.65 (2.75) $n = 154$
Hamilton Anxiety Scale (score)	18.79 (7.10) $n = 256$	21.78 (8.70) $n = 488$	21.26 (8.80) $n = 215$	24.26 (8.47) $n = 174$	9.62 (7.60) $n = 233$	10.92 (8.52) $n = 429$	10.93 (8.41) $n = 185$	12.09 (8.72) $n = 154$
Hamilton Depression Scale (score)	12.25 (5.47) $n = 256$	14.46 (7.17) $n = 487$	14.43 (7.20) $n = 215$	15.51 (6.81) $n = 174$	6.58 (5.53) $n = 223$	8.13 (6.98) $n = 429$	8.05 (6.61) $n = 185$	8.80 (6.63) n 154
Work and social disability (1–5)	3.21 (0.99) $n = 254$	3.90 (0.89) $n = 485$	4.03 (0.83) $n = 215$	3.89 (0.87) $n = 174$	2.29 (1.15) $n = 223$	2.81 (1.25) $n = 426$	2.95 (1.22) $n = 185$	2.78 (1.25) $n = 154$
Physician Rated Global Improvement	–	–	–	–	7.65 (1.99) $n = 223$	7.53 (2.04) $n = 428$	7.36 (2.06) $n = 185$	7.69 (1.90) $n = 154$
Patient Rated Global Improvement	–	–	–	–	7.55 (2.05) $n = 222$	7.41 (2.11) $n = 426$	7.17 (2.18) $n = 185$	7.58 (1.97) $n = 154$

Outcome at endpoint was not significantly different between the three age-of-onset groups after controlling for baseline differences, center effects, degree of avoidance behavior and medication effects on treatment response in GLM type 1 analyses (see Table 4). The same results were seen in the completer analyses (week-8 comparison), which are therefore not given in a separate table.

Non-hierarchical GLM type III analyses did not reveal a significant main effect for the grouping variables (chronology between panic disorder and avoidance behavior, age of onset) on any baseline or outcome measures. The interactions in the model which involved the grouping variable did not reach significance (adjusted for multiple tests, $P < 0.01$).

Discussion

Our Investigation comes up with Four Major Findings

(1) A considerable number of patients develop avoidance behavior before a fully diagnosable panic disorder is present. In the majority of cases this will be only limited phobic avoidance, but in one third of the group we find full agoraphobia before panic disorder. Part of the problem lies in the definition of onset of panic disorder, which is not the age of the first panic attack but the age when the diagnostic criteria are met for the first time. However, our finding is in line with reports from epidemiological studies on the existence of agoraphobia without panic disorder (Myers et al. 1984; Robins et al. 1984). Nonetheless, at a time when the patients meet all the criteria for panic disorder the group with "avoidance first" is no different in treatment response. Obviously, patients can manifest avoidance behavior and become agoraphobic with fewer panic attacks than are necessary for the diagnosis according to DSM-III. In the DSM-III-R (APA 1987), this criterion has been changed so that patients with only one panic attack can receive a diagnosis of panic disorder when the attack is followed by a period of at least a month of persistent fear of having another attack.

(2) The age of onset in panic disorder is often outside the range given in the DSM-III-R. However, age at onset of panic disorder does not define subgroups which differ in short-term response to drug treatment. Similar findings have been reported for other psychiatric conditions, such as early versus late-onset bipolar illness (Taylor and Abrams 1981) and early-onset versus late-onset geriatric depression (Greenwald and Kramer-Ginsberg 1988), and for long-term outcome of adolescent versus adult onset of mania (McGlashan 1988).

(3) The identification of an early-onset group (before age 20) may still prove to be useful, because the association with agoraphobia, a severe and disabling complication, calls for diagnosis and intervention at the earliest possible stage. Psychiatrists should be aware of the possibility of an onset of panic disorder during childhood. As in patients with depression, where early onset is associated with a higher risk for substance abuse (Christie et al. 1988), early-onset panic disorder may also involve a

Table 3. Basic characteristics of comparison groups defined by age of onset on panic disorder (early, medium, late onset)

	Early		Medium onset		Late		
	n	(%)	*n*	(%)	*n*	(%)	
Sex							
Male	80	(38.65)	161	(36.84)	190	(38.38)	Chi-spuare = 0.3
Female	127	(61.35)	276	(63.16)	305	(61.62)	$df = 2$, n.s.
Subtype							
Panic disorder uncomplicated	31	(15.20)	99	(22.80)	127	(25.20	Chi-square = 25.1
Panic disorder with limited avoidance	77	(37.75)	161	(37.10)	228	(45.25)	$df = 4$, $P = 0.0001$
Panic disorder with agoraphobia	96	(47.05)	174	(40.10)	149	(29.55)	
Medication							
Alprazolam	66	(30.28)	153	(34.62)	167	(32.87)	Chi-square = 1.5
Imipramine	77	(35.32)	147	(33.25)	167	(32.87)	$df = 4$, n.s.
Placebo	75	(34.40)	142	(32.13)	174	(34.26)	

Table 4. Baseline and outcome characteristics for patients with early, medium and late of onset of panic disorder

	Baseline [Mean (SD)]			Endpoint [Mean (SD)]		
	Early	Medium onset	Late	Early	Medium onset	Late
No. of spontaneous panic attacks (log)	1.07 (1.47) $n = 204$	1.19 (1.45) $n = 431$	1.17 (1.50) $n = 499$	1.31 (0.36) $n = 180$	1.08 (0.34) $n = 375$	1.31 (0.36) $n = 435$
Anticipatory anxiety (% of time)	44.53 (29.82) $n = 204$	44.25 (32.02) $n = 430$	40.75 (33.79) $n = 497$	20.70 (26.61) $n = 180$	16.55 (22.28) $n = 374$	16.36 (25.50) $n = 434$
Global phobia score (1–10)	6.51 (2.64) $n = 204$	6.09 (2.91) $n = 431$	5.94 (2.95) $n = 499$	3.73 (3.00) $n = 180$	3.32 (2.74) $n = 375$	3.08 (2.82) $n = 435$
Hamilton Anxiety Scale (score)	21.46 (8.31) $n = 204$	20.60 (8.28) $n = 430$	22.03 (8.73) $n = 499$	10.39 (7.76) $n = 180$	10.51 (7.82) $n = 376$	11.25 (9.01) $n = 435$
Hamilton Depression Scale (score)	14.43 (6.84) $n = 204$	13.24 (6.32) $n = 429$	14.74 (7.22) $n = 499$	7.63 (6.13) $n = 180$	7.39 (5.92) $n = 376$	8.39 (7.26) $n = 435$
Work and social disability (1–5)	3.87 (0.92) $n = 203$	3.78 (0.95) $n = 429$	3.71 (0.96) $n = 496$	2.85 (1.31) $n = 180$	2.71 (1.20) $n = 374$	2.66 (1.25) $n = 434$
Physician Rated Global Improvement	–	–	–	7.51 (1.97) $n = 180$	7.60 (1.79) $n = 374$	7.52 (2.21) $n = 435$
Patient Rated Global Improvement	–	–	–	7.31 (1.93) $n = 180$	7.47 (1.88) $n = 374$	7.44 (2.31) $n = 433$

comparable complication. We could not test for this possible association, because the study design called for exclusion of patients with substance abuse problem. In family studies on panic disorder the identification of an early-onset subgroup may be useful to define a more homogeneous subgroup, as in research on depression, which has shown that early onset in the proband leads to increased risk of depression in relatives (Weissman et al. 1986).

(4) Clinicians must know that panic disorder can start later in life. Although the diagnosis may be more difficult, because of a higher prevalence rate of somatic disorders that can mimic panic attacks (e.g. heart disease), a correct psychiatric diagnosis may be crucial for an effective therapy.

According to the results in this study, the short-term efficacy of either imipramine or alprazolam (and placebo response) does not depend on the age of onset. Given that both active drugs have a comparable potential in the treatment of all aspects commonly seen in panic disorder, medication can be chosen with respect to its specific side-effect profile. Therefore, a tricyclic antidepressant such as imipramine maybe the drug of choice in younger individuals because of a lower liability to cause dependence. When imipramine is not indicated because of its cardiovascular side-effects, which may be the case in older patients, substitution by alprazolam seems possible. However, the potential of all benzodiazepines to cause ataxia and the higher risk of bone fractures on falling in elderly patients should be considered, as well as

the problem of dependence when the drug is given to this age group.

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