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Angst, J ; Gamma, A ; Baldwin, D S ; Ajdacic-Gross, V ; Rössler, W

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ORIGINAL PAPER

Jules Angst · Alex Gamma · David S. Baldwin · Vladeta Ajdacic-Gross · Wulf Rössler

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Abstract *Background* Generalized anxiety disorder (GAD) is generally considered to be a chronic condition, waxing and waning in severity; however prospective investigation of the course of GAD in community samples is lacking. This study seeks to fill that gap, by identifying the whole spectrum of generalized anxiety syndromes, sub-typing them according to their duration and frequency of occurrence, and evaluating their long-term course and outcome in the community. *Method* The prospective Zurich Study assessed psychiatric and somatic syndromes in a community sample of young adults ($N = 591$) (aged 20 years at first interview) by six interviews over a period of 20 years (1979–1999). GAD syndromes were defined by DSM-III symptom criteria without applying any exclusion criteria. A spectrum of generalized anxiety was defined by duration: 6 months (DSM-IV), 1 month (DSM-III), ≤2 weeks (with weekly occurrence over one year), and anxiety symptoms. From 1978 (screening) to 1999 the annual presence of symptoms and treatment was assessed. Persistence of anxiety was defined by the almost daily presence of symptoms over the previous 12 months. *Results* The annual incidence of DSM-III GAD increased considerably between the ages of 20 and 40. The average age of onset of symptoms was 15.6 years; in 75% of cases it occurred before the age of 20. 75 of 105 DSM-III GAD cases had at least one follow-up. At their individual last follow-up, 12 of those 75 subjects (16%) were re-diagnosed as having GAD, 22 (29%) manifested subthreshold syndromes or anxiety symptoms, while 39 cases, the majority, (52%) were symptom-free; 5 of the 12 re-diagnosed GAD cases were persistent (corresponding to 7% of all 75 initial GAD cases). In their twenties they were treated at some time in 6% of all years, but in their thirties this figure rose to 12%. At their individual last follow-up 26% of 6-month GAD subjects and 22% of 1-month GAD subjects were still being treated. Treated *vs.* non-treated subjects did not differ in terms of gender but did differ in severity, persistence and in comorbidity with bipolar-II disorder, social phobia, obsessive-compulsive syndromes and substance-use disorders. *Limitations* Results are based on a relatively small sample and cannot be generalized to adults aged over 40 years. *Conclusions* The course of DSM-III-defined GAD may not be chronic, as previously suggested, but mainly recurrent with intervening symptom-free periods of recovery in about half of cases. Over a period of 20 years there was more improvement than progression within the anxiety spectrum.

Key words generalized anxiety disorder · incidence · onset · course · outcome · anxiety spectrum

J. Angst (✉) · A. Gamma · V. Ajdacic-Gross
W. Rössler
Zurich University Psychiatric Hospital
Lenggstrasse 31
P.O. Box 1931, 8032 Zurich, Switzerland
Tel.: +41-44/384-2611
Fax: +41-44/384-2446
E-Mail: jangst@bli.unizh.ch

D.S. Baldwin
Clinical Neuroscience Division, School of Medicine
University of Southampton
Southampton, UK

Introduction

Generalized anxiety disorder (GAD) is generally considered to follow a chronic course, waxing and waning in severity [1, 9, 24, 28]. GAD was observed to be chronic for a decade or longer [22] with deteriorations during times of stress [1, 15].

Barlow et al. [10] found that GAD patients tended to spend more time being anxious than did patients with panic disorder, a finding compatible with the observations of Anderson et al. [2]. From a five-year follow-up study of GAD patients, Woodman et al. [30] reported that only 18% had remitted. Comorbid GAD subjects are reported to manifest higher disability and dysfunction than 'pure' cases, i.e. without comorbidity [19, 26]. In the National Comorbidity Survey, the course of GAD and its related impairment were not connected with comorbidity with major depression [20], which supports the independence of GAD as an independent diagnostic entity.

However the results of the 'Harvard/Brown Anxiety Disorders Research Program', a large 8-year follow-up study of GAD and panic patients recruited from 11 psychiatric clinics are at variance with the cited evidence for the chronicity of GAD. Yonkers et al. [31] reported remission rates cumulatively for every year of follow-up. After five years, 35% of men and 38% of women with GAD showed full symptomatic remission, and after 8 years the proportions were 46 and 56%, respectively. Most remissions occurred within the first 2 years. More recently Bruce et al. [13] published a further follow-up of the same sample over 12 years: 58% of GAD cases had recovered, while the probability of recurrence in recovered patients was 45%. Comorbidity with other psychiatric disorders worsened the prognosis, with lower recovery and higher recurrence rates. A remarkable remission rate of 50% was also found in retrospect by Blazer et al. [12] in three Epidemiologic Catchment Area Study sites. Furthermore, in a recent 40-year follow-up study of 59 GAD patients, only about 17% of patients were re-diagnosed as having GAD, which tended to disappear at around the age of 50 years [25].

This paper seeks to add the evidence provided by prospective epidemiological data from the Zurich Study on the course of the GAD spectrum over 20 years (subjects aged 20/21 to 40/41). It seems reasonable to anticipate that the long-term prognosis of GAD in a cohort of subjects from community settings may be better than that of treated psychiatric patients. We will also compare 1-month GAD (reflecting DSM-III criteria) with 6-months GAD (reflecting DSM-IV criteria), in terms of course and outcome.

Methodology

Sample selection and design of the study

The Zurich Study (a prospective epidemiological study of depressive, neurotic and psychosomatic syndromes) was based at outset on a sample of 4,547 subjects (m = 2,201; f = 2,346) representative of the canton of Zurich in Switzerland in 1978 (population 1.1 million). All subjects were screened with the Symptom Checklist 90-R (SCL-90-R) [16], a comprehensive self-report questionnaire of 90 questions, which has been validated for that purpose and covers a broad range of psychiatric symptoms. This investigation took place in 1978 when the male participants were aged 19 years (at conscription) and the females 20 years (at enrolment on the electoral register). They were approached with the authorisation of the government and the Departments of the Interior of their cantons of residence.

In order to enrich the sample with cases at risk for the development of psychiatric syndromes, a stratified sampling procedure was chosen: a sub-sample of 591 subjects (292 males, 299 females) was selected for interview, with two-thirds consisting of high scorers (i.e. above the 85th percentile) on the Global Severity Index of the SCL-90, and one-third being a random sample of those with lower scores (i.e. below the 85th percentile). The stratified sample represents, after weighting, 2,600 persons of the same age from the general population. The theoretical basis of these stratified procedures is described by Dunn et al. [17]. In our sample there were no major differences in socio-demographics between males and females.

Details of sampling procedures and refusal rates were presented in the first publication [3] and recently again [6]. Since screening in 1978, six interview waves have been conducted: in 1979 (ages 20/21), 1981 (22/23), 1986 (27/28), 1988 (29/30), 1993 (34/35) and 1999 (40/41).

Interviews

The structured psychopathological interview and rating of social consequences of psychic disturbances for epidemiology (SPIKE) was used [3]. The SPIKE assesses a series of somatic complaints, including insomnia, headache, and gastrointestinal, cardiovascular, respiratory, perimenstrual and sexual syndromes. It also assesses depression, hypomania, anxiety, phobias, obsessive-compulsive and fatigue syndromes, eating disorders, post-traumatic stress disorder, substance abuse and suicidal phenomena. Each interview covered the previous 12 months and was carried out in the subjects' homes with their informed consent, and in accordance with the Declaration of Helsinki.

Validity and reliability testing have been carried out with particular reference to depression and anxiety [6]. All subjects were approached for each interview (by letters informing them about the study and guaranteeing medical secrecy), regardless of whether or not they had participated in previous interviews, unless they had explicitly stated their wish to withdraw from the study definitively.

Interviewers were mainly graduate clinical psychologists plus some psychiatrists, both groups having had special interview training. The inter-rater reliability of the SPIKE was found to be high, with kappas of 0.89 and 0.91 for the symptoms of depression and anxiety and of 0.90 for the corresponding syndromal diagnoses. Further methodological details were published by Angst et al. [6]. 62.1% of the original sample remained in the study across 20 years, with the following participation rates: 47% in all six interviews; 63% in five interviews; 74% in four interviews; 82% in three interviews, and 91.4% in at least two interviews. Those who dropped out of the study did not differ significantly from those who remained until the most recent interview (1999) in terms of stratified sampling and of most demographic characteristics [18].

Diagnostic classification

Since 1980 the definitions of GAD have undergone considerable modification with successive versions of the DSM and ICD. There is substantial doubt about some of these changes [15]. In the case of GAD it has been demonstrated that duration, e.g. one month (DSM-III, ICD-9) or six months (DSM-III R, DSM-IV and ICD-10), was not a relevant diagnostic criterion and did not reduce the degree of comorbidity with depression [5, 11, 21]. Furthermore, application of the 6-month criterion for GAD excludes about half of all patients treated for the disorder in the general population; moreover, the varying syndrome definitions in the above diagnostic manuals merely describe the same symptom complex in different ways [5].

For this reason we defined a GAD syndrome, independently of its duration, using DSM-III symptom criteria, i.e. by the presence of 3 of 4 symptom domains: motor tension, autonomic hyperactivity, apprehensive expectation, vigilance and scanning. Exclusion criteria were not applied. The shorter or milder manifestations of anxiety existing under the temporal diagnostic threshold of DSM-III GAD (1-month) are taken into account in this paper in order to describe their transitions into diagnostic cases and vice versa. We found some subjects with 2-week GAD syndromes and many more with highly recurrent brief episodes of anxiety, termed recurrent brief anxiety (RBA) [8]. The diagnosis of RBA required the presence of a DSM-III GAD syndrome of under 2 weeks' duration (in fact, usually only a few days) and high recurrence (at least monthly, over 1 year).

For the purposes of this study the *GAD severity spectrum* was defined by duration: 1 = GAD 6 months, 2 = GAD 1 month, 3 = GAD 2 weeks, 4 = RBA, 5 = anxiety symptoms, 6 = no symptoms. DSM-III-R GAD of 6 months' duration could not be diagnosed until the 1993 and 1999 interviews (subjects aged 34/35 and 40/41), because the concept did not exist earlier. DSM-IV GAD could be diagnosed in 1999 but no follow-up data is available yet.

Course and outcome

Over the 22 years from 1978 to 1999 the presence or absence of symptoms and treatment was assessed on the basis of "yes/no" replies for every year; in order to correct for drop-outs, the intra-individual % years were computed. In all six interviews anxiety was assessed with a stem question and a list of symptoms; a symptom-free status was also defined in this way. In addition, at every interview subjects were given the Symptom Check List 90R (SCL-90-R), which measures several aspects of anxiety with the sub-scales of anxiety, somatisation, phobia, obsessive-compulsive, and interpersonal over-sensitivity. Mean scores on the scales of anxiety and somatisation will also be given as measures of outcome.

In addition, *persistent* GAD syndromes were defined from 1986 to 1999 (ages 27/28–40/41) by the "almost daily" presence of anxiety symptoms in the previous year and a minimum duration of the episode of 3 months (1986, 1988) or 6 months (1993, 1999). *Non-persistent* GAD syndromes comprise every GAD syndrome with a minimum length of 2 weeks (RBA not included). We reserve the term "chronic" for the description of the longitudinal course of anxiety episodes over the whole study period. A *chronic* course means the repeated occurrence of diagnostic or subdiagnostic anxiety syndromes, whereas a *recurrent* course means the full recovery or merely residual symptoms between episodes.

Statistics

Frequencies were compared using χ^2—tests. Kruskal-Wallis tests were used on continuous and rank-ordered data. The percentage of years suffered or treated was intra-individually compared between the first and second decade of the Zurich Study using Wilcoxon sign-rank tests. A multivariable logistic regression was used to compare treated to non-treated GAD cases in terms of comorbidity. The initial full model was reduced by step-wise elimination of the least significant predictor variable, until all remaining predictors were significant at $P < 0.10$.

The follow-up of the first episode of GAD was analysed as follows: firstly, the first episode of 1+ month GAD was identified for each subject who had ever had such an episode. The interview year of the first episode could vary inter-individually. In a second step, all subsequent interviews of a given subject were examined for the occurrence of any anxiety state or symptom-free state. The occurrence of any category of anxiety state was recorded: "no anxiety symptoms", "anxiety symptoms", "RBA", "2-weeks GAD", or "1+ month GAD". Thus, the reported percentages (Fig. 2, left-hand side) refer to the percentage of subjects with a first episode of 1+ month GAD having had a particular anxiety state at any subsequent interview. As various categories of anxiety state can follow the initial episode of GAD, those percentages total more than 100%. The analysis of the follow-back of the last individual episode of 1+ month GAD was carried out analogously. Analyses were done in Stata 8.2 and SAS 8.2 for Windows.

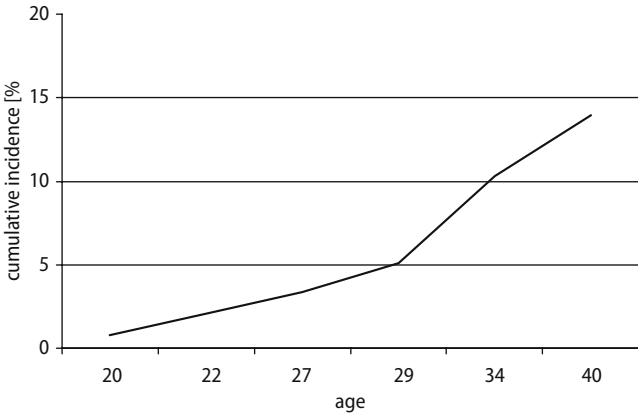

Fig. 1 Cumulative incidence rates of DSM-III GAD from age 20/21 to 40/41 years

Results

The overlap between DSM-III GAD, RBA and panic attacks

After adjustment for gender and stratified sampling, all three diagnostic groups were significantly associated with each other: 1-month GAD was associated with both panic attacks (41%; OR = 2.3) and RBA (35%; OR = 1.7). Although recurrent brief anxiety (RBA) was assessed and defined in the context of GAD, it was strongly associated (55%; OR = 8.1) with panic attacks. As a consequence of this finding, RBA has been included in another report as a sub-diagnostic element of the panic spectrum, but has not been excluded from the GAD spectrum in the present paper.

Incidence and age of onset of anxiety in subjects with DSM-III GAD (1979–1999)

The one-year prevalence rates of DSM-III GAD increased from 0.8% at age 20/21+2.5% at age 29/30 and 6.4% at age 40/41; the cumulative incidence rates for the six interviews are 0.8% at age 20/21, 2.1% at age 22/23, 3.4% at age 27/28, 5.1% at age 29/30, 10.3% at age 34/35, and 14.0% at age 40/41 (Fig. 1).

The *age of onset of anxiety symptoms* was 15.6 years. There was no difference between the subgroups of the GAD severity spectrum. Over 75% of GAD cases manifested their first GAD symptoms before the age of 20/21 years. Women prevailed in all subgroups of the GAD spectrum (Table 1).

Table 1 Incidence, age of onset and course of GAD syndromes (1–4) and anxiety symptoms (5)

	GAD syndromes				Anxiety sympt.	Others[a]		
	6 months	1 month	2 weeks	RBA			*P*	
	1	2	3	4	5	6	1–6	1–4
Subjects (N)	31	74	23	91	169	203		
Males	11	32	7	35	81	126		
Females	20	42	16	56	88	77	0.0002	0.0001
F/M ratio	1.8	1.3	2.3	1.6	1.1	0.6		
Cumulative incidence (%)	3.2	10.8	2.5	8.7	27.9	47.0		
Males	2.5	9.7	0.6	5.2	24.0	58.1		
Females	3.9	11.8	4.3	12.2	31.7	36.3	0.0001	0.0001
F/M ratio	1.6	1.2	7.9	2.3	1.6	0.6		
Age of onset of anxiety sx.								
Mean (SD)	13.2 (7.3)	16.5 (8.4)	15.5 (6.5)	14.4 (7.0)	17.5 (7.4)	14.7 (8.0)	0.001	0.13
Median	13.5	18	18	15	19	14		
Q1–Q3	7–18	8–20	12–20	8–20	12–21	8–20		
% years symptomatic (mean, SD)								
1978–1999 (22 years)	50.9 (26.2)	36.0 (23.9)	47.2 (25.3)	45.6 (28.2)	25.6 (21.0)	6.4 (13.3)	0.0001	0.06
1978–1988 (11 years)	40.8 (27.9)	35.7 (27.2)	41.8 (28.3)	48.8 (30.5)	29.1 (25.6)	7.1 (14.6)	0.0001	0.84
1989–1999 (11 years)	61.9 (33.8)	33.7 (30.3)	51.1 (35.1)	34.4 (37.4)	16.3 (24.0)	1.9 (8.7)	0.0001	0.003
% years treated (mean, SD)								
1978–1999	15.1 (18.3)	6.5 (10.1)	14.1 (25.5)	10.4 (15.8)	3.6 (8.3)	0.1 (1.1)	0.0001	0.14
1978–1988	9.6 (16.7)	3.7 (8.0)	10.1 (23.3)	9.9 (17.8)	2.6 (7.0)	0.0 (0.0)	0.0001	0.65
1989–1999	19.4 (25.3)	9.7 (16.3)	17.4 (29.3)	8.8 (19.0)	3.8 (11.8)	0.3 (2.7)	0.0001	0.25
Lifetime treatment rate for anxiety	71.0	56.8	56.5	53.9	33.7	4.4	0.0001	0.42
Persistent anxiety (weighted prevalence)	2.7	1.4	0	0.9	0.6	0		
At individually last interview								
Number of days in previous year with anxiety symptoms (median)	360	50	32.5	35	14	0	0.0001	0.0001
Number of days in previous year with anxiety or panic symptoms (median)	360	50	32.5	30	14	2	0.0001	0.0001

[a]Others include also subjects with anxiety symptoms occurring outside of the interview years (lifetime prevalence was not assessed)

Course of GAD

Annual presence of symptoms and treatment across 22 years

Subjects with DSM-III GAD suffered from anxiety in 41.4% (median 37.5%) of all 22 years in which symptoms were assessed, and were treated for anxiety in 8.9% (median 4.5%) of all years. Comparing the two decades 1978–1988 and 1989–1999, we found that the percentage of symptomatic years among DSM-III GAD subjects increased non-significantly from 38.7% (±29.5) in the third decade of life to 43.0% (±34.3) in the fourth decade of life ($P < 0.12$), and the percentage of years with treatment increased significantly from 6.1% (±12.2) to 12.0% (±20.0) ($P < 0.02$). Table 1 shows the results for 6-month and DSM-III GAD separately. On comparing the four GAD groups, there was no clear difference or systematic trend showing 6-month GAD to be more symptomatic or more likely to be treated than 2-week GAD, between the ages of 20 and 40 years.

Follow-up and follow-back of DSM-III GAD

Subjects could receive a GAD diagnosis at any interview during the prospective study. The average follow-up period of the 105 GAD subjects was 7.6 (SD = 6.45) years, with a median of 6.0 years.

Follow-ups to age 34/35 and 40/41: During the first five interview waves (up to age 34/35) 83 DSM-III GAD cases were identified cumulatively, 62 of whom were followed up until the age of 40/41, when only 18% still met diagnostic criteria, 5% manifested GAD syndromes shorter than 1 month, 24% had residual symptoms and 53% were symptom-free.

At the age of 34/35 (1993) 20 cases of DSM-III-R GAD (6 months' duration) were diagnosed and 14 of them were followed-up until the age of 40/41: 57.1% had become symptom-free, 14.3% manifested symptoms, 14.3% were diagnosed as DSM-III GAD and 7.1% as 6-month DSM-III-R GAD; a residual 7.1% had developed RBA.

Follow-up to the individual last interview: 75 cases of 1+ month GAD had at least one follow-up interview. At their individual last follow-up, 12 of those 75 cases (16%) still received a 1+ month GAD diagnosis, 22 (29%) were diagnosed with 2-week GAD, RBA or anxiety symptoms, but the majority of 39 cases (52%) were symptom-free. The mean duration of follow-up of the 75 cases was 10.6 years (median = 11 years, SD = 5.1, range 2–20 years).

Figure 2 indicates all movements between subgroups on the GAD spectrum across the six inter-

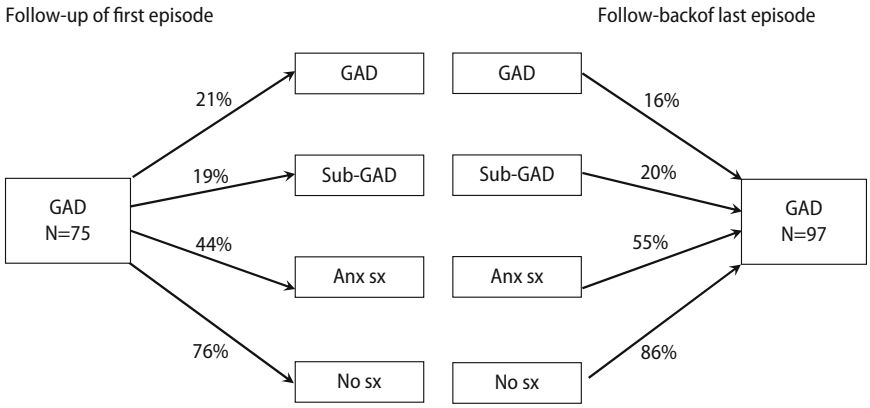

Fig. 2 Follow-up of individually first and follow-back of individually last episode of 1+month GAD. The categories are not mutually exclusive in order to show all changes

views (each covering 12 months). Of the 75 cases of 1+ month GAD who were re-interviewed at least once, 21% again manifested GAD, 19% sub-threshold syndromes and 44% symptoms, but the majority of those 75 cases (76%) were also symptom-free at one or other subsequent interview. These figures illustrate the considerable movement between the subgroups over time. A similar finding is obtained by following back subjects' last episodes of 1+month GAD.

Transition between subgroups of the GAD spectrum

The temporal pattern of the changes within subgroups of the GAD spectrum is shown in more detail in Fig. 3. For this purpose waves1 (age 20/21) and 2 (age 22/23) and waves 3 (age 27/28) and 4 (age 29/30) were unified. Most changes were from a symptom-free status to a diagnostic subgroup and vice versa, which may be interpreted as a recurrent course along the GAD spectrum with symptom-free intervals.

Across the four age groups (20/23; 27/30; 34/35; 40/41) the stability of DSM-III-defined GAD increased from 9 to 21%, interpretable as a growing trend to recurrence or chronicity in GAD subjects. After the ages of 30 and 34/35, 7 and 11% respectively of RBA (brief GA syndromes) had developed into DSM-III GAD five years later. These findings are compatible with the increased annual incidence rates described above.

Improvement and deterioration of anxiety: On our GAD severity spectrum comprising four categories (no symptoms, symptoms, subthreshold syndromes <1 month, 1+ month GAD), subjects were observed to move up- and downwards over time. This change in severity was analysed by comparing the individual first and last completed interviews; longitudinally 138 cases showed an improvement, 110 cases a deterioration and 128 subjects no change at all. The remaining 215 subjects never manifested anxiety symptoms and were not included in this calculation. A histogram showing the distribution of changes is

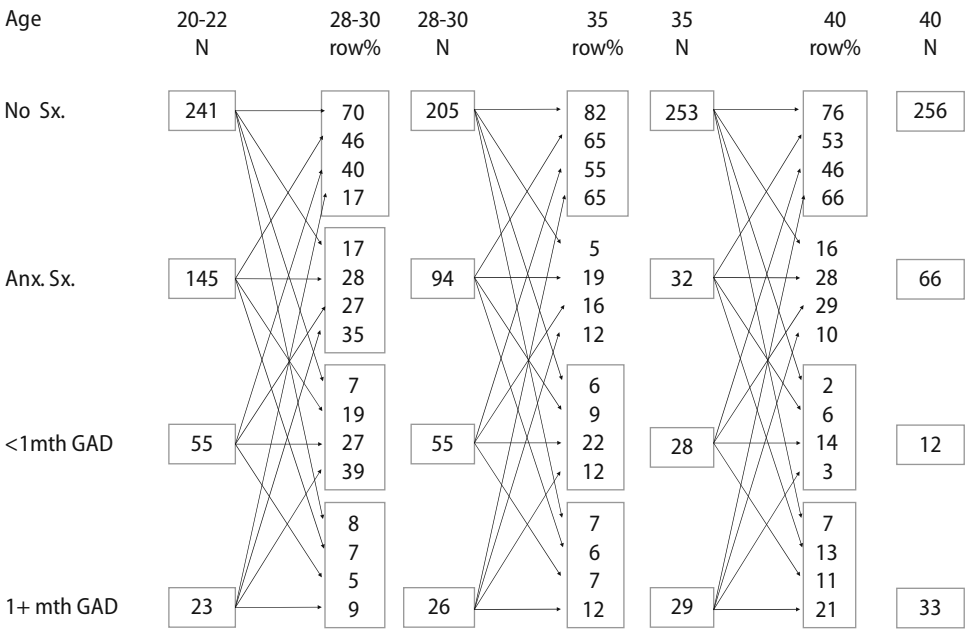

Fig. 3 Temporal shifts within the GAD spectrum

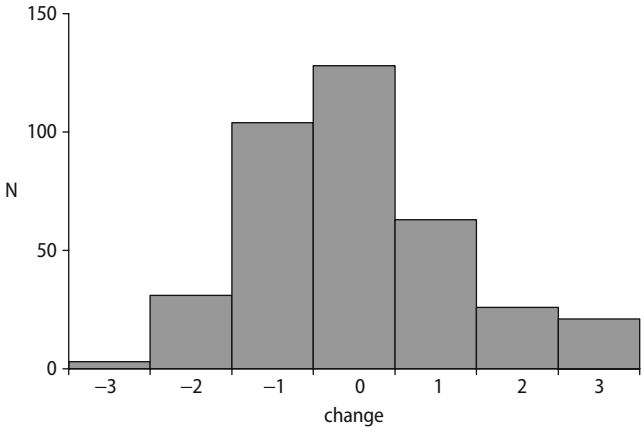

Fig. 4 Histogram of changes in anxiety subgroup between first and last completed interview. The first interview for all subjects was the one completed at age 20; the last completed interview differed for different subjects. The change was quantified in terms of units corresponding to the change of one subgroup of anxiety to the next more or less severe subgroup. Subgroups in order of ascending severity are "no anxiety", "anxiety symptoms", "<1 month-GAD", and "1+ month GAD". As an example, a subject who changed from "no anxiety" at his or her first interview to "1+ month GAD" at his or her last interview would be assigned a change of +3. A subject who changed from "<1 month-GAD" at the first to "anxiety symptoms" at the last interview would be assigned a change of −1

given in Fig. 4. Most common were no change or a switch to the nearest less severe category of the anxiety spectrum. Overall, then, the condition in most subjects either did not deteriorate or even improved.

Persistence of GAD

A key question investigated by this paper is whether GAD is persistent. Here, 'persistence' was defined as the presence of anxiety symptoms almost every day during the twelve months prior to an interview. At the individual last interview 5 of 75 (7%) 1-month DSM-III GAD cases had become persistent, and 1 of 14 (7%) 6-month DSM-III-R GAD cases diagnosed at age 34/35 years had become persistent at the age of 40/41 years.

As regards the stability of persistence: 30 subjects with DSM-III GAD met the persistence criterion at least once; during the follow-up 27 (90%) of them showed no further persistence, and in only one of the remaining three subjects was GAD always persistent, whereas the other two changed status repeatedly. Of further interest is the follow-up of 10 cases of persistent 6-month DSM-III-R GAD diagnosed at the age of 34/35 years: all had ceased to meet the criteria for persistence at the age of 40/41 years.

Social conditions and treatment at the individual last follow-up

Subjects with GAD syndromes had a higher income than those with no GAD diagnosis (including symptom carriers and symptom-free subjects) (Table 2). They were more often married, separated or divorced than controls and more often suffering from a chronic physical disease. In addition, the 6-month GAD group followed over 5 years did not differ in social outcome variables from other subgroups of the GAD spectrum except, again, by a higher income. A similar proportion of subjects with 6-month and 1-month GAD were being treated at the last follow up: 6-month GAD: 25.8% and DSM-III GAD: 21.6% (Table 2).

Treated vs. non-treated DSM-III GAD

Treatment was defined as treatment for GAD syndromes by MD's or psychologists. 67 (58%) of GAD subjects were professionally treated over their lifetime. There was no gender difference, either in raw numbers or in weighted prevalence rates between treated and non-treated groups (Table 3). Persistent anxiety was twice as frequent among treated subjects (48%). The latter were also symptomatic over more years than non-treated subjects (50.5% vs. 26.7% of the 22 observed years). Treated subjects felt significantly more distressed and more impaired at work by their anxiety.

Among those who had been treated, the condition of 52% worsened between their first and last individual interviews, whereas 22% improved and 27% did not change. The corresponding figures for subjects who had never been treated for GAD were 49% (worse), 20% (improved) and 32% (no change).

Table 3 shows the much higher overall comorbidity among treated than among untreated GAD subjects. However, comorbidity with major depressive disorder did not differ significantly between treated and untreated individuals and even showed a trend in the opposite direction.

A multivariable logistic regression including as predictors sex and the diagnoses unipolar depression, bipolar II disorder (BP-II), social phobia, obsessive-compulsive syndrome, binge eating, alcohol abuse or dependence, cannabis abuse or dependence, and tobacco abuse or dependence found significantly higher odds for BP-II (OR = 2.9, 95% C.I. 1.03–8.32, $P < 0.04$) and social phobia (OR = 3.7, 95% C.I. 1.22–11.07, $P < 0.02$), and a trend to higher odds for cannabis abuse/dependence (OR = 4.0, 95% C.I. 80–19.96, $P < 0.10$) in treated compared to non-treated GAD cases.

Discussion

We used a spectrum approach to describe the course of GAD, with analysis of the movements between four subcategories: DSM-III GAD, subthreshold GAD (<1 month), anxiety symptoms and no symptoms. A comparable approach was used in long-term studies

Table 2 Social variables at individually last interview

	6-months GAD 5	1-month GAD 4	<1 month GAD/RBA 3	Anx sx 2	No sx 1	*P* 1–5
N	31	74	114	169	203	
Lives alone	25.8%	21.6%	19.3%	17.8%	16.3%	0.67
Part time employed	48.3	52.4	44.6	38.2	17.3	0.001[a]
Fully employed	51.7	47.6	55.4	61.8	82.7	
Housewife	29.0	32.4	32.5	33.1	16.3	0.001
Receives benefits	15.4	13.8	13.2	14.8	7.6	0.58
Income[b]						
<1,500 CHF	6.7	0	0	2.2	1.5	0.14
<2,500 CHF	0	3.3	10.0	9.8	18.9	
<4,000 CHF	13.3	10.0	22.0	16.3	16.7	
>4,000 CHF	80.0	86.7	68.0	71.7	62.9	
Any chronic illness	51.6	40.5	34.7	39.5	22.0	0.002
Never married	29.0	33.8	43.0	33.1	52.7	0.0007
Ever divorced or separated	35.5	17.6	18.4	13.0	9.4	0.002
Treated	25.8	21.6	13.9	9.2	0	0.0001

[a]Interaction with sex significant ($P = 0.001$): less women are fully employed
[b]Only for employed subjects ($N = 324$); an ordered logistic regression model showed significant increases in income in subjects with 1+month GAD (OR=3.2 [1.7–6.0]) compared to non-symptomatic subjects, adjusted for sex and employment status. Female sex, even when corrected for employment status, was associated with lower incomes (OR = 0.35 [0.19–0.65])
CHF = SWISS FRANCS

of depressive disorders [7, 19]. As a subthreshold syndrome, the *GAD spectrum* also includes recurrent brief anxiety, which was earlier found to form a bridge to panic attacks [5].

The prevalence data illustrate that GAD syndromes of 1–5 months' duration and brief manifestations under 2 weeks are much more common than syndromes lasting 6 months or more. We concentrated on DSM-III 1-month GAD syndromes because this enabled us to analyse the course across 20 years from 1979 to 1999: in addition, this subgroup has been shown in clinical terms to be as valid as using a sub-group with 6-month GAD. In an earlier analysis [5] we found, in agreement with two other epidemiological studies, that generalized anxiety syndromes of varying length (2-weeks, 1 month, 3 and 6 months) were homogeneous and did not differ significantly in terms of treatment rates, impairment, distress, family history or comorbidity with major depressive episodes, bipolar disorder or suicide attempts [11, 21]. Further research based on new epidemiological samples is needed to clarify whether a minimum duration of 2 weeks of anxiety could be used as a diagnostic cut-off. The treatment rates and years with treatment found in our study would be compatible with this shorter temporal criterion, as originally used in the Research Diagnostic Criteria. The minimum duration for GAD was extended from 1 month (DSM-III) to 6 months (DSM-III-R, DSM-IV) in order to reduce the association with major depression, however the *association of GAD with major depressive episodes* has been shown to be independent of the duration of GAD [5].

On the diagnostic level the *cumulative incidence* rate of GAD increased after the age of 30 years, confirming the results of larger epidemiological studies [14, 29] which describe a positive correlation of onset with age. This is compatible with the findings of Carter et al. [14], who reported an increase in the annual prevalence rates up to the age of 55 years. In our younger age group DSM-III GAD was very common. By contrast Wittchen [27] found that GAD is uncommon before 25 years of age which may partially be a consequence of the 6-month criterion of DSM-III-R and DSM-IV. We can hypothesise that in adulthood, age may be associated with an increasing incidence of GAD. The *onset of characteristic anxiety symptoms* (not diagnoses) occurred in 75% of GAD cases before 21 and tended to be earlier in 6-month GAD (median 13.5 years) than in 1-month GAD (18 years, $P < 0.13$, but note the small numbers).

75 of 105 diagnosed GAD cases had at least one follow-up. Like major depression the *course* of GAD was recurrent in the majority of cases: in at least one follow-up interview, 21% were diagnosed again as GAD, 19% manifested sub-diagnostic anxiety syndromes, and 76% were symptom-free (numbers not mutually exclusive). Across all interviews only one case of DSM-III GAD and no cases of DSM-IIIR GAD were always persistent.

The *final outcome* at the individual last follow-up was persistent (chronic) in only 7% of DSM-III and DSM-III-R GAD cases. For a considerable proportion of them the outcome was favourable: of 75 subjects previously diagnosed as having DSM-III GAD 58% had been symptom-free for at least 1 year at the age of 35 years, and 63% at the age of 40 years. For the few

Table 3 Treated LT (life-time) versus non-treated GAD

	DSM-III GAD			*P*	
	Treated LT (1)	Non-treated (2)	Others[b] (3)	(1–3)	(1–2)
N	67	38	486		
Males	27	16	249		
Females	40	22	137	0.16	0.86
Cumulative incidence	6.1%	7.8%	86.1%		
Males	5.3	6.9	87.8		
Females	6.9	8.7	84.4	0.05	0.89
Treated 1986–1999 by					
Psychiatrist	20.9	–	2.3		
G.P.	19.4	–	5.6		
Psychologist	11.9	–	3.1		
Distress 0–100 (means, s)	86.0 (14.1)	65.6 (21.9)		.	0.0000
Impaired at work 0–100	44.4 (32.4)	19.9 (23.7)			0.0003
Medication[a] (81–99)	35.8	5.3	6.9	0.0001	0.002
None	64.2	94.7	93.1		
Antidepressants (86–99)	23.9	7.9	6.6	0.0001	0.05
Benzodiazepines[a] (86–99)	7.5	–	2.0	0.02	0.09
% years w. symptoms	50.5 (24.4)	26.7 (20.6)	22.7 (25.3)	0.0000	0.0000
Median	52.9	20.5	13.6		
Q1–Q3	31.8–68.2	12.5–36.4	0.0–33.3		
Persistent anxiety	47.8	23.7			0.02
Outcome at individual last interview				0.0001	0.41
GAD	38.8	42.1	0.0		
Sub-threshold GAD	9.0	5.3	5.5		
Anxiety symptoms	17.9	7.9	15.4		
No symptoms	34.3	44.7	79.1		
Comorbidity					
Major depr. disorder	22.4	31.6	15.2		0.30
Bipolar-II disorder	40.3	15.8	11.5		0.004
Social phobia	34.3	13.2	11.5		0.02
Obs.-compulsive syndrome	38,8	23.7	15.6		0.12
Binge eating	25.4	7.9	11.7		0.03
Alcohol use disorder	35.8	21.2	19.1		0.12
Cannabis weekly	19.4	5.3	26.1		0.05
Any drug abuse	47.8	21.1	10.1		0.007

[a]Self-medication
[b]Subjects without a diagnosis of GAD

6-month DSM-III-R cases followed-up from 35 to 41 the findings did not differ: 8 of 14 cases (57%) became symptom free. The relatively good outcome of GAD in our epidemiological study is comparable with the 12-year patient follow-up study of Bruce et al. [13] mentioned in the introduction. These results are clearly at odds with the common affirmation that GAD has a generally chronic course, but are compatible with the description of a waxing and waning course: however our data show that waning is more common than waxing.

As expected, *treated GAD* subjects were more severely affected than non-treated subjects in terms of distress, impairment at work and persistence of the disorder. Surprisingly, there was no gender difference in lifetime prevalence rates between treated and non-treated subjects. The finding that treatment of GAD was associated with comorbidity was not surprising. Bipolar-II disorder was much more strongly associated than MDD with treated GAD, a finding compatible with the close association of BP-II with anxiety disorders [4].

Limitations

The study sample is relatively small and there was an attrition rate of 38.5% over 20 years of observation. Our group of DSM-III-R GAD subjects was too small ($N = 16$) and their follow-up over only 6 years too short to allow definitive conclusions, but our preliminary findings suggest their course did not differ from those for DSM-III GAD. The course of GAD in subjects older than 40 years may be worse than that in younger adults.

Conclusions

Our 20-year prospective follow-up data on (1-month) DSM-III-defined GAD demonstrate a recurrent course of the disorder with a chronicity rate of under 20%. These results question the current rather pessimistic view that the disorder has a generally chronic course,

and suggest there may be room for therapeutic optimism as proposed by Helen Lester and Linda Gask [23]. At the same time, the degree of recurrences illustrate the need to develop effective long-term prophylactic strategies.

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