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Prediction of outcome in neurotic disorder: a 5-year prospective study

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ABSTRACT

Background. There have been no previous studies of the outcome of different neurotic disorders in which a prospective group with original randomization to treatment have been followed up over a long period. Such studies are important in identifying the factors associated with good and poor outcome.

Methods. A 5-year follow-up assessment was made of a cohort of 210 psychiatric out-patients seen in general practice psychiatric clinics with a DSM-III diagnosis of generalized anxiety disorder (71), panic disorder (74) or dysthymic disorder (65) and randomized to drug treatment, cognitive and behaviour therapy, and self-help. A total of 182 of the patients (87%) were assessed after 5 years by examination of hospital and GP records using a standardized procedure and outcome determined with a four-point outcome scale.

Results. One hundred and seven (60%) of the patients had a favourable outcome but the remainder continued to be handicapped either intermittently or continuously throughout the 5-year period. Analysis of the value of initial data in predicting outcome using polychotomous step-wise logistic regression revealed that five variables were significant predictors of poor prognosis: older age; recurrent episodes; the presence of personality disorder at entry; general neurotic syndrome at entry; and symptom severity after 10 weeks. The initial DSM diagnosis and original treatment given, together with ten other variables, were of no predictive value.

Conclusions. The long-term outcome of neurotic disorder is better predicted by age, personality and recency of onset than by other clinical variables with the exception of initial response to treatment.

INTRODUCTION

It has long been difficult to pronounce on the diagnosis and management of neurotic disorder. Many forms of classification have been presented and guidelines given about the best forms of management. Use of these has been limited by the knowledge that a large proportion of people presenting with neurotic symptoms (which include many with adjustment disorders) appear to have a good outcome irrespective of intervention (Greer & Cawley, 1966; Mann *et al.* 1981; Dunn, 1983; Bronisch, 1991), that this improvement is rapid and largely takes place within a 1-year period (Coryell *et al.* 1994) and has been claimed to be more dependent on social rather than clinical factors (Huxley *et al.* 1979; Goldberg *et al.* 1990; Brown *et al.* 1992; Goldberg & Huxley, 1992). However, interpretation of these studies may have been unduly favourable since so many were carried out at a single follow-up point and made no measurement of continuing morbidity. To counter this there is also evidence that a significant proportion between one-fifth and one-third of all the main neurotic disorders, have symptoms and disability which persist in the longer term (Van Valkenburg *et al.* 1984; Lelliott *et al.* 1987; Keller & Hanks, 1994; Katschnig *et al.* 1995;

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Roy-Byrne and Cowley, 1995). With this conflicting evidence it is important to determine whether good or poor outcome can be predicted early as this has clear implications for management.

The value of the new diagnostic system for neurotic disorder in prediction of outcome is also uncertain and has been handicapped by the shortage of studies that examine outcome in several neurotic disorders simultaneously. There is also uncertainty about the best measures of outcome in these disorders and whether continuous or single assessments are preferable. With the exception of major depressive illness, in which clear definitions have been made of remission and relapse (Frank *et al*. 1990), other related disorders have a mixture of symptomatic and social outcome that are inconsistent. The prediction of outcome and response to treatment is an important public health issue. We need to know what proportion of the 7–10% of the total population suffering from anxiety and depressive symptoms at any one time (Kessler *et al*. 1994; Meltzer *et al*. 1994) need intervention, and which of the 200 per 1000 at risk presenting in primary care (Goldberg & Huxley, 1992) require specialized care. The factors that predict good and poor outcome should help in identifying those who most need intervention. We, therefore, carried out a 5-year follow-up of a cohort of patients with specific neurotic disorders seen originally in general practice psychiatric clinics to determine the factors identified at initial or post-treatment assessment that best predicted outcome.

METHOD

The main design is described fully elsewhere (Tyrer *et al*. 1988). Drug-free patients presenting at psychiatric clinics in general practice with either generalized anxiety disorder, panic disorder or dysthymic disorder were randomly allocated to one of three main treatment policies; drug treatment, cognitive and behaviour therapy (CBT), and self-help. By means of constrained randomization patients were allocated so that after 210 had entered the study 84 received drug treatment, 84 received CBT and 42 received self-help. During the first 10 weeks of the study the drug group was divided equally into three, dothiepin (28 patients), diazepam (28) and placebo (28). All treatments were given for 6 weeks and then reduced gradually so that at 10 weeks all patients had completed their course of treatment. Subsequently, if further therapy was required in the drug group it was preferentially given in the same mode, initially with antidepressants in the form of dothiepin; other psychotropic drugs could also be given at the clinician's discretion. Those allocated to CBT were advised to continue psychological treatment preferentially in the form of cognitive therapy, and if additional sessions of CBT were not effective other psychological treatments could be given. The self-help group was advised of the dangers of dependence on both drugs and therapists and encouraged to use self-help approaches throughout the subsequent 2 years.

Exactly 5 years after original referral a research doctor (H.S.) attempted to examine the medical records of all patients included in the study. She contacted both mental health units and general practice surgeries and, if permission was given, visited to record the details of all treatments received and to make a judgement of overall outcome using a standardized scale used in a previous investigation of psychiatric morbidity in general practice (Seivewright *et al*. 1991). This recorded the cause of death, if the patient had died during the period of follow-up, numbers of contacts with all health professionals for psychiatric disorder and also contacts with the general practitioner for non-psychiatric conditions, the number and length of psychiatric admissions and day-hospital attendance, all psychotropic drugs treatment received and total time drug-free during the 5 years. Private medical consultations were not recorded but constituted a very small proportion of total contacts in this population, who used the NHS services almost entirely. After examination of all sources of information H.S. summarized the mental health outcome into five categories. The most severe of these (outcome 5) was 'no time well during follow-up with frequent contact, or death from deliberate self-harm'. Because only nine patients scored at level 5 this was merged with level 4 for purposes of analysis (Table 1). The scores were made without any previous knowledge of the patients and the classification of outcome checked independently with another author (P.T.), who examined 10 sets of records and scored them all similarly.

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Table 1. *Global outcome in* 182 *patients with neurotic disorders after* 5 *years*

Code	Description	Number of patients *N* (%)
1	Very good: no psychiatric contact with either general practice or psychiatric services since initial period of care (up to 9 months)	50 (27)
2	Good: some contact for psychiatric problems in general practice or psychiatric clinics but at least half time well	57 (31)
3	Fair: frequent contact with services for psychiatric problems for more than half of time of follow-up but intensity of care not great (e.g. short period of day-care, many out-patient contacts but no in-patient care)	38 (21)
4	Poor: little or no time in follow-up period well. Intermittent contact as out-patient or day-patient	28 (15)
5	Very poor: continuously ill with frequent contact with all parts of psychiatric services or death from deliberate self-harm	9 (5)
	Total	182

Although it was appreciated that examination of records alone was not a substitute for direct contact with the patient, and that the outcome recorded was a 'service outcome' only, the population studied was one that does not normally avoid contact with health care services. Examination of the data up to 2 years showed that service outcome at that time correlated well within clinical outcome recorded by rating scales (Tyrer *et al*. 1993) the mean symptom scores using the CPRS were 8·9 at 2 years in the 50 patients rated 1 on the outcome scale corresponded with 11·8, 15·0 and 20·8 for the other three levels of severity (a difference that was significant (using one-way analysis of variance) at the 0·1% level).

Analysis of data

Polychotomous (forward and backward) stepwise logistic regression models were used to evaluate the influence of pretreatment factors on global outcome. These models are a natural extension of the standard logistic model for binary (yes/no) outcomes to ordered outcomes i.e. they have more than two categories with a natural ordering but no specific numerical interpretation (Ashby *et al*. 1989; Surtees & Barkley, 1994). For example, in the present study the outcome has four categories ordered from very good to poor/very poor (or vice versa). Statistically, the log (odds) on a specific outcome (e.g. better than outcome level 2 ('good')) is modelled in the usual linear regression fashion as the sum of an intercept and the product of each independent variable (covariate) multiplied by the corresponding regression coefficient. The polychotomous logistic regression model has a different intercept for each level (except for the most extreme since there is no better outcome than very good), but forces the regression coefficients for the covariates to be the same for all levels.

Mathematically,

$$\log(\text{odds of an outcome better than level } j) = a_j + b_1 x_1 + b_2 x_2 + \ldots + b_k x_k$$

where a_j is the intercept for the level j, x_1, $x_2 \ldots$, x_k are k covariates, and b_1, $b_2 \ldots, b_k$ the corresponding regression coefficients. The model estimates the J − 1 intercepts (where there are J levels for the ordered outcome) and k regression coefficients together with their standard errors.

Sixteen pre-treatment factors (covariates) (Table 2) were identified as possible predictors; age, sex, marital status (married, single, separated or divorced or widowed), social class (with classes 1 and 2 combined as there were only eight patients in social class 1), randomized treatment group (drug, psychological treatment and self-help) (Tyrer *et al*. 1988); original DSM-III diagnosis (dysthymic, generalized anxiety and panic disorder), duration of symptoms, new episode or recurrence, precipitating factors – (1) none, (2) loss (job, separation, death of friend or relative (not first-degree), imprisonment), (3) conflict (major illness or operation, occupational stress, conflicts with others, physical assault, court appearance, financial stress), and (4) addition events (Jacobs *et al*. 1974) (extramarital affair or new serious relationship, proposal of marriage, move to new address, unwanted pregnancy), personality disorder classified by type using the PAS classification (Tyrer & Alexander, 1979), severity of personality disorder (dichotomous separation into personality disorder *v*. no personality disorder using the PAS), the presence or absence of the general neurotic syndrome (GNS) (a score of $\geqslant 4$ on the general neurotic syndrome scale) (GNSS) (Tyrer,

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Table 2. *Characteristics of sample of* 182 *patients completing assessments*

Characteristic	*N* (%)*
Age (years)	
Median	36
(25, 75)	(27, 43)
Sex	
Male	55 (30)
Female	127 (70)
Marital status	
Married	78 (43)
Separated, divorced, widowed	47 (26)
Never married	57 (31)
Social class	
I and II	24 (13)
III	36 (20)
IV	72 (40)
V	50 (28)
Treatment	
Drugs	76 (42)
CBT (cognitive/behaviour therapy)	71 (39)
Self-help	35 (19)
Initial diagnosis	
Dysthymia	53 (29)
GAD (generalized anxiety disorder)	62 (34)
Panic disorder	67 (37)
Duration of symptoms (weeks)	
Median	80
(25, 75)	(28, 208)
Episode	
New	120 (66)
Recurrent	62 (34)
Precipitating factors	
None	40 (22)
Loss	44 (24)
Conflict	69 (38)
Addition events	29 (16)
Personality disorder (PD)	
No	116 (64)
Yes	66 (36)
Severity of personality disorder	
None or personality difficulty	117 (64)
Personality disorder	65 (36)
General neurotic syndrome	
$\leqslant 3$	90 (49)
$\geqslant 4$	92 (51)
CPRS	
Median	21
(25, 75)	(17, 28)
CPRS at 10 weeks	
Median	12
(25, 75)	(7, 23)
CPRS difference (entry – 10 weeks)	
Median	7
(25, 75)	(1, 14)
MADRS	
Median	18
(25, 75)	(13, 25)
BAS	
Median	19
(25, 75)	(16, 25)
Number of initial SCID diagnoses	
1	44 (24)
2	81 (45)
3	36 (20)
$\geqslant 4$	21 (11)

* Except where quartiles are given.

1989), initial scores on total psychopathology (Comprehensive Psychopathological Rating Scale (CPRS)) (Åsberg *et al.* 1978), depression (MADRS) (Montgomery & Åsberg, 1979) and anxiety (BAS) (Tyrer *et al.* 1984) sections of the scale, and the number of additional DSM-III psychiatric diagnoses present at original presentation identified by a structured interview (SCID) (Spitzer & Williams, 1983). Two post-treatment factors, CPRS at 10 weeks and the change in (transformed) CPRS scores between baseline and 10 weeks were also included; the first as a measure of initial post-treatment psychopathology and the second reflecting the change in psychopathology over this period. Age, social class, duration of symptoms (logarithmically transformed), the rating scales (CPRS, MADRS and BAS), and the number of SCID diagnoses (all four square-root transformed after the addition of one) were continuous covariates. The transformations were used to normalize skewed distributions. Analysis was conducted with BMDP program PR (polychotomous stepwise logistic regression).

RESULTS

A total of 182 of the patients (87% of the total sample) had data recorded. The 26 patients with no information comprised five who had died, seven who had changed addresses and could not be traced, six whose general practitioners refused consent and eight whose records were so patchy that outcome could not be adequately assessed (including one who gave a false name at initial assessment). An additional two patients were excluded because they did not have CPRS scores available at 10 weeks or at 6 weeks (when they could have been carried forward). The baseline characteristics of the 28 excluded were very similar to those of the 182 seen (Table 2) but there was a higher proportion of non-completers with dysthymic disorder (12, 43%) than other initial diagnoses, those allocated to cognitive and behaviour therapy (13, 46%) and from social class V (10, 36%). Thirty seven (20% of 182 seen) had changed address in the 5 years, including nine who had moved out of the Nottingham area. Three patients had CPRS scores at week 6 carried forward to week 10 because the latter were not recorded. The five

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who had died included one who committed suicide by overdose 15 weeks after entry to the study and four who died from natural causes (congestive cardiac failure, myocardial infarction, gastric carcinoma and status epilepticus).

Table 2 summarizes the characteristics of the sample analysed; these show that the sample was a representative one of neurotic disorder, with a greater proportion of women and those from social classes IV and V, two-thirds of the disorders were new episodes, and one-third of the patients had personality disorder. By 5 years of follow-up just less than a third of patients had had no psychiatric contact and consequently were rated as having a very good outcome (Table 1); by contrast one-fifth had been unwell for most of the time.

Univariate analysis (not shown) suggested that six covariates were of potential prognostic importance ($P < 0{\cdot}10$), age at entry, new or recurrent episode, severity of personality disorder, GNS status, CPRS at 10 weeks and change in CPRS between entry and 10 weeks. The full model including all covariates simultaneously except for CPRS at entry (which is determined exactly by CPRS at 10 weeks and the change in CPRS from entry to 10 weeks) identified age only. After backward elimination of variables just age, (OR (95% CL): 1·5 (1·2, 1·9); $P < 0{\cdot}001$) and CPRS at 10 weeks (1·6 (1·3, 1·9); $P < 0{\cdot}001$) were retained. The combined results of these analyses consequently suggest that the odds on poorer outcome increase with age, recurrent episodes, the presence of personality disorder and presence of general neurotic syndrome at entry, and psychopathology at the end of treatment.

Since the modelling above incorporates only the main effect of each covariate, which by itself provides no information about possible interactions, further exploratory analyses were conducted using five of the potential prognostic factors identified above. Inclusion of the change in CPRS at entry and end of treatment was considered unnecessary because of its association with the latter. The analysis was also simplified further by dichotomizing both age and CPRS at their medians instead of modelling them as continuous variables.

The five covariates together with all interactions between them (up to second order, i.e. 3-factor) were then included in a backwards elimination regression analysis retaining those significant at $P = 0{\cdot}05$. Higher order interactions were not considered because of difficulty in interpretation; interactions involving variables not identified in the initial analysis were not considered because of the limited size of the data-set. The resulting model (Table 3) included interactions between age at entry and recurrent episode ($\chi^2 = 5{\cdot}86$, df = 1, $P = 0{\cdot}016$), and between personality disorder and general neurotic syndrome ($\chi^2 = 4{\cdot}36$, df = 1, $P = 0{\cdot}037$) as well as CPRS at 10 weeks ($\chi^2 = 12{\cdot}7$, df = 1, $P < 0{\cdot}001$) (Table 3).

Age above the median (36 years) in combination with a recurrent episode increases the odds on poorer outcome by a factor of 2·4 over a younger patient with a new episode (and other covariates unchanged); the combination of

Table 3. *Summary of final model – odds ratios for poorer outcome*

Covariate	Odds ratio (95% CL)
Age*	1·00 (0·52, 2·0)
Recurrent episode (RE)	0·57 (0·23, 1·4)
Age × RE	4·20 (1·30, 14·0)
Personality disorder (PD)	0·81 (0·36, 1·8)
GNS (General neurotic syndrome)	0·71 (0·34, 1·5)
PD × GNS	3·28 (1·10, 10·0)
CPRS at 10 weeks*	2·88 (1·59, 5·2)

* Dichotomized at the median.

Table 4. *Percentages in two outcome categories according to selected levels of five risk factors under a polychotomous logistic regression model*

Age (years)	Episode	PD	GNS	CPRS	Outcome (%) Fair/poor (3 and 4)	Outcome (%) Poor (4)
< 36	New	No	No	⩽ 12	27	10
< 36	New	No	No	> 12	51	25
⩾ 36	Recurrence	No	No	⩽ 12	47	22
⩾ 36	Recurrence	No	No	> 12	72	44
< 36	New	Yes	Yes	⩽ 12	41	18
< 36	New	Yes	Yes	> 12	67	38
⩾ 36	Recurrence	Yes	Yes	⩽ 12	63	35
⩾ 36	Recurrence	Yes	Yes	> 12	83	60

Risk factors measured at baseline except for CPRS assessed at end of treatment (i.e. 10 weeks): PD (personality disorder), GNS (general neurotic syndrome).

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personality disorder and general neurotic syndrome increases them by a factor of 3·7; and a CPRS above 12 at 10 weeks increases them by 2·9 over a CPRS of 12 or less. Table 4 shows how the percentages with poor outcome, or fair/poor outcome, increase with the presence of selected combinations of the five risk factors.

DISCUSSION

In discussing the implications of the findings it is important to stress that the cohort of patients analysed was intermediate between those seen in primary care only and those referred to out-patient psychiatric services, and is therefore not typical, and cannot be equated with the patients seen in some other studies who have been recruited as in-patients (Kerr *et al*. 1974; Krieg *et al*. 1987). However, we feel that our sample is a good representative of those with neurotic disorders as it includes people with symptoms and distress of sufficient severity to lead to concern in the general practitioner and consequent referral; it is also more likely to be a representative sample of such patients as stigma is less in the general practice setting and the sample is less prone to selection bias than the equivalent group in an out-patient setting. The introduction of general practice psychiatric clinics in Nottingham led to a small increase in referrals (Tyrer *et al*. 1990*a*) and much of this was due to more of those with neurotic disorders being referred.

The overall outcome of this population, like that of an equivalent depressive one, can also be summarized as 'future imperfect' (Surtees & Barkley, 1994), with 60% having an essentially good outcome and 40% being handicapped to a significant extent through persistent or recurring symptoms. Outcome measures in anxiety disorders are less well-defined than in depressive ones (Rush & Weissman, 1991) and in our outcome classification the occasional contact with a (mainly primary) care worker and limited intervention was still regarded as essentially a favourable one.

Five of the variables examined were predictive of long-term outcome; age, recurrent episodes, response to initial assessment and treatment, personality status (particularly severity) and the general neurotic syndrome. The evidence that older patients presenting with neurotic symptoms have a worse outcome is consistent with other evidence in follow-up studies of depression (Surtees & Barkley, 1994) and is perhaps insufficiently known in clinical practice. We know that neurotic symptoms in childhood frequently resolve entirely and have a generally good outcome (Robins, 1966; Tyrer & Tyrer, 1974; Kovacs *et al*. 1984) and our findings suggest that this prognosis extends beyond adolescence into early adult life. Conversely, older patients with neurotic symptoms have been noted to have a high incidence and persistent symptomatology (Larkin *et al*. 1992) and this too is consistent with our findings.

The initial response to assessment and treatment was a surprisingly good predictor of long-term outcome. This measurement, 10 weeks after base-line assessment, represents only one-fiftieth of the outcome period and yet was a major predictive influence. Although it would be easy to assume that patients who responded well to appropriate treatment would be likely to have a good outcome overall it is important to stress that all patients were randomized to the five treatments and that one of these was placebo medication, suggesting that there were intrinsic elements of early response independently of treatment (perhaps regression to the mean). This may suggest that such early responders have adjustment disorders primarily and that if these were recognized better by the general practitioner (Casey, 1997) unnecessary referral could be avoided.

Our finding that personality status was an important clinical indicator of outcome is consistent with other recent evidence (Duggan *et al*. 1990; Shea *et al*. 1990; Reich & Vasile, 1993; Quinton *et al*. 1995; Surtees & Wainwright; 1996) and adds weight to the advice to make a full assessment of personality status as soon as possible after initial psychiatric contact to enable good prediction of long-term outcome to be made. Patients with co-morbid mental state and personality disorder tend to have greater levels of symptomatology than those with mental state disorder alone (Tyrer *et al*. 1990*b*, 1997) but the assumption that the association with personality disorder is merely an epiphenomenon of greater severity is not supported as symptom levels alone were not predictive of outcome (Table 2).

The additional finding that the presence of the general neurotic syndrome adds to the predictive

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power of the model (Table 3) gives some support to the concept that such a syndrome is an important core feature of neurosis characterized by mixed anxiety–depressive features and dependent or obsessional personality (Larkin *et al*. 1992; Tyrer *et al*. 1992 (equivalent to the anxious-fearful personality cluster C in the DSM notation). The finding that the presence of both personality disorder and the general neurotic syndrome increases the risk of a poor outcome threefold shows that anxiety–depression comorbidity and personality dysfunction is a powerful combination for persistent handicap and is much greater than the identification of personality disorder alone.

The evidence that the general neurotic syndrome confers better prediction than personality disorder diagnosis alone suggests that the specific identification of dependent and obsessional features of personality abnormality (the anxious–fearful cluster (C) in the DSM classification) and the presence of mixed anxiety–depressive diagnosis and family history as a similar disorder all contribute to poor prognosis.

The negative predictors are at least as informative as the positive ones. In particular, the initial diagnostic group (dysthymic, generalized anxiety and panic disorder) contributed nothing of importance to the prediction of outcome (Table 2) and to some extent was unexpected. In the first 10 weeks of the study dysthymic disorder showed some evidence of a poorer outcome than the other groups (Tyrer *et al*. 1988) and this might have been expected over the longer time scale, not least because the duration of symptoms necessary for the diagnosis of dysthymic disorder (symptoms present more often than not over the past 2 years) is much less than those for DSM-III generalized anxiety disorder (symptoms present for most of the last 6 months) and panic disorder (three or more panic attacks in a 3 week period). However, neither duration of symptoms nor precipitating factors were predictive factors (Table 2) and so it appears that successful prediction in these disorders is decided more by identifying the features of vulnerability to relapse rather than dissection of symptom profiles or their persistence.

The fact that very similar outcomes were found in all three diagnostic groups does not in itself invalidate their classification. However, as in our study the treatment allocated to all groups were randomized initially and largely maintained at 2 years (Tyrer *et al*. 1993) and so outcome could not therefore be influenced by initial treatment, the finding illustrates the close relationship between anxiety and depressive disorders identified in many previous studies, the loss of their distinguishing characteristics in follow-up and the importance of their comorbidity (Van Valkenburg *et al*. 1984; Vollrath & Angst, 1989; Stein *et al*. 1990; Angst & Vollrath, 1991; Starcevic *et al*. 1994). From a longitudinal perspective the separation of the three diagnostic groups is of little value and emphasizes the value of recording the outcome of several disorders simultaneously rather than the current tendency to examine it in one disorder only, particularly prevalent in panic disorder (Roy-Byrne & Cowley, 1995).

The findings of this study reinforce a volume of evidence that is now getting too large to ignore, that the current classification of neurotic disorders is of little clinical value. Prediction of outcome now joins the list of other factors of clinical importance, pathognomonic clinical features, response to treatment and likely complications, that conspicuously fail to discriminate between the disorders identified by the classification (Tyrer, 1990). A review of this part of nosology is overdue.

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