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Subtypes of Panic Attacks and ICD-9 Classification

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Summary. No single ICD-9 category corresponds to panic disorder (DSM-III). To investigate whether patients with panic attacks can be identified by means of ICD-9, 97 patients with three panic attacks within 3 weeks were recruited from various medical centers, and were classified independently according to DSM-III and ICD-9.

The ICD-9 diagnoses were scattered over a broad range of categories, and it was impossible to identify patients with panic disorder in this manner. Anxiety state, affective psychosis, and depressive neurosis were the most frequent ICD-9 diagnoses. The boundary between affective psychosis on the one hand and anxiety state and depressive neurosis on the other hand was validated by present and previous symptomatology and by cluster analysis. The boundary between anxiety state and depressive neurosis could not be validated in this way. Correspondingly, modifications of the ICD-9 classifications are proposed.

Key words: Panic attacks – Classification – ICD-9 – DSM-III – Anxiety neurosis – Depressive neurosis – Affective psychosis – Cluster analysis

Introduction

Panic disorders have been validated by genetic transmission [19] and by response to special treatments. It has been demonstrated that panic attacks can be treated efficaciously with imipramine or phenelzine [12, 13]. Thus it is of clinical importance to identify patients with panic attacks by particular primary or secondary diagnoses or by combinations of them. Accordingly, the diagnosis panic disorder has been included in DSM-III [1]; but patients with panic attacks due to several other conditions (e.g., due to a major depressive episode) are not classified as panic disorder. However, some empirical findings indicate that panic attacks should always be classified as panic disorder [15]. Therefore, in a revised version of DSM-III layed down in the Structured Clinical Interview for DSM-III (SCID-UP) [18] all patients with panic attacks are classified as panic disorders, if they have a sufficient number of symptoms during the attacks and sufficient frequency of attacks.

The diagnosis "panic disorder" is not included in ICD-9 [22], instead, panic anxiety is cited under the frame of anxiety state. However, ICD-9 includes no guide for making diagnoses; therefore, patients with panic attacks may or may not be classified as anxiety neurosis and patients with anxiety neurosis may or may not have panic attacks according to ICD-9.

Panic attacks are heterogeneous with respect to associated features and they are considered to be heterogeneous in respect to course and to pathogenesis. The ICD-9 diagnosis can be expected to reflect this heterogenity. Thus it can be expected that patients with panic attacks are often classified not only as anxiety state (German translation: anxiety neurosis) but also e.g., as depressive neurosis or as affective psychosis. Yet, additional diagnoses are possible according to ICD-9, but there is no necessity in ICD-9 to classify patients with prominent panic attacks as anxiety states. Therefore, it may be difficult to identify patients with panic attacks within the framework of ICD-9. This necessitates a systematic investigation of the ICD-9 classification of patients with panic attacks.

This task may be done by comparing the ICD-9 and DSM-III classification of patients with panic attacks. No study relating ICD-9 and DSM-III diagnoses of patients with panic attacks has been published up to now. Therefore, we investigated the relationship between both diagnostic schedules in a sample of patients representative of treated patients with panic attacks; furthermore, we investigated sources of the diagnostic variance according to the ICD-9 classification. We were interested in the relationship between subtypes of panic attacks (referring to avoidance behavior, the history of depressive disorders, associated syndromes), with the ICD-9 classification.

Empirical classification (cluster analysis) may be used as a way of validating clinical diagnoses [6, 17]. Therefore, an empirical classification of patients with panic attacks was performed and related to the ICD-9 classification.

Methods

1. Subjects

Patients were recruited from several private practices, three outpatient departments at the university hospital of Mainz, and the department of psychiatry. All patients treated within a 3-month period by these facilities were referred if they reported suffering from at least one discrete period of apprehension or fear within the last 3 weeks, and if they stated a positive history of a least three panic attacks in the past with at least one panic attack weekly in this period ($n = 122$). Cases of acute organic diseases have been excluded from the study. Likewise, all patients who had not experienced at least three panic attacks within a 3-week period and were therefore not meeting criterion A for panic disorder were excluded ($n = 7$).

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Another 18 patients were excluded because of a diagnosis of schizophrenia, paranoid disorder, psychotic disorder not elsewhere classified (DSM-III) or a schizoaffective disorder (RDC).

Thus, 97 patients were included in our analyses; these patients were classified as panic disorder according to SCID.

2. *Assessments*

2.1 Interviews. Each patient was interviewed separately on two different occasions by a trained psychiatrist using structured diagnostic interviews: (a) the SCID [18] which was followed by additional questions in order to assess patients on the Anxiety-Depression-Discrimination Scale designed by Gurney et al. [11] and according to Feighner Criteria [7], and (b) the Diagnostic Interview Schedule (DIS) and additional questioning relating to present state and previous history.

2.2 Diagnostic Classification. DSM-III diagnoses were performed on the bases of the SCID rating.

In SCID, a further manner of classification of panic attacks is recommended: a diagnosis of panic disorder is given in spite of the presence of a major depressive episode (MDE), of agoraphobia, of obsessive-compulsive disorder, or of somatization disorder.

A MDE developing prior to or simultaneously with panic attacks is called a primary MDE. A MDE developing at least 2 months later than the first panic attack is called a secondary MDE. The concepts of primary and secondary MDEs are only aimed at the temporal relationship between panic attacks and MDE and thus are not identical with the corresponding concepts of Feighner et al. [7].

Furthermore, classification was carried out according to the Gurney Anxiety-Depression-Discrimination Scale and according to anxiety or phobic neuroses (Feighner Criteria).

A diagnosis of "chronic anxiety" was given to patients who met positive criteria for present generalized anxiety (DSM-III) with disregard to exclusion criteria and with a duration of at least 2 years (determined by SCID).

"Chronic depression" was diagnosed when a patient met positive criteria for present dysthymic disorder (DSM-III) with disregard to exclusion criteria but with a minimum duration of 2 years (SCID rating).

Data from the DIS rating and additional free questions served for the performance of the ICD-9 diagnoses (life-time diagnosis). Also, disorders excluding patients from the study (schizophrenia, paranoid disorder, psychotic disorder not elsewhere classified (DSM-III), and schizoaffective disorder (RDC)) were diagnosed by means of the DIS.

3. *Raters*

All structured interviews were conducted by one of five experienced psychiatrists who had completed a joint training in the use of the SCID with 15 patients with mixed states of anxiety in order to establish reliability. In the last 5 interviews, perfect agreement was attained for the diagnoses of panic disorder, agoraphobia, and MDE (DSM-III).

ICD-9 diagnoses were performed independently from the SCID interview by one of eight experienced psychiatrists who had participated for the last 2 years in weekly joint sessions for the training of diagnostic accuracy with regard to ICD-9 classification.

4. *Statistical Analyses*

1. Comparisons between different groups were performed by Fisher's exact test, or the χ^2 test – if necessary with Fisher-Yates adjustment – for binary data, and by the Kruskal-Wallis test for ordinal or metric data. When pairs of groups were compared simultaneously Bonferroni adjustment for empirical P values was applied [10].
2. For validation of clinical ICD-9 diagnoses [17], empirical classification was performed by cluster analysis of cases applied to present and previous symptomatology (associated present and previous syndromes of anxiety, phobia and depression relevant for diagnostic classification as listed in Tables 3 and 4 – ordinal scaled data were dichotomized at median) assessed in the SCID interview of the total sample ($n = 97$).

The problems in applying cluster analysis are: (a) the choice of the clustering procedure and the statistical method for determination of the membership of a cluster, (b) the determination of the number of clusters. Therefore, dealing with problem (a) we applied three methods simultaneously (K-means procedure with two initial conditions as nonhierarchical methods and Ward's procedure as hierarchical method) as proposed by Mezzich [16], Garside and Roth [8], and Everitt [5]. Dealing with problem (b) we determined the optimal number by the stopping rule of Andreasen and Grove [2] based on Ward's method: proceed in joining the two closest clusters from the initial position of 97 cluster; stop, when the error-sum of squares becomes greatly compared with the last several joining. According to this optimal number of clusters, the Ward's cluster analysis and the two version of the K-means cluster analysis (i.e., two different initial positions, one without any initial partition, and one with an initial partition in 2 parts by chance) were carried out.

For assuring the stability of the resulting clusters, only those patients were included in a particular cluster who were classified in this cluster by all three methods. Thus, we received only robust clusters.

Cluster analysis was carried out using the Clustan package [21].

Results

1. *Frequencies of ICD-9 Diagnoses*

Of the 97 patients recruited 91 received only one ICD-9 diagnosis which is listed in Table 1. There were 6 patients who re-

Table 1. ICD-9 Diagnoses of patients with panic attacks and one ICD-9 diagnosis only ($n = 91$)

300.0	Anxiety neurosis	30
300.1	Hysteria	5
300.2	Phobic disorders	1
300.3	Obsessive–compulsive disorder	1
300.4	Neurotic depression	15
296.x	Affective psychosis – currently depressed	25
303.0	Alcohol dependence syndrome	2
305.0	Nondependent abuse of drugs	1
306.8	Other specified psychophysiological malfunction	2
308.9	Acute reaction to stress	1
309.1	Prolonged depressive reaction	1
301.x	Personality disorders	5

Table 2. Convenient ways of subclassification of panic attacks in relationship to prevailing ICD diagnoses

ICD diagnosis/ Subtypes	Anxiety state ($n = 30$)	Affective psychosis ($n = 25$)	Neurotic depression ($n = 15$)	
DSM III Classification of panic attacks:				
Panic disorder	16	16	5	
Agoraphobia with panic attacks	13	2	9	
Not classified in either category	1	7	1	**
SCID Classification				
without avoidance behavior	10	13	5	
with limited avoidance behavior	15	8	7	
with extensive avoidance behavior	5	4	3	N.S.
Classification according to Feighner Criteria:				
Anxiety neurosis	6	0	3	
Phobic neurosis	11	4	8	
Not classified in either category	13	21	4	**
Classification according to the Gurney Scale:				
Anxiety	29	12	14	
Depression	1	13	1	**
Classification according to history of MDE:				
Primary MDE (DP)	1	14	1	
Secondary MDE (PD)	14	8	9	
Without a history of MDE (P)	15	3	5	**

*, **: Significant deviation from association due only to chance ($P = 0.05$, $= 0.01$)

ceived two ICD diagnoses, with anxiety state (ICD-9 300.0) the most frequent ($n = 4$). For avoiding interactions between ICD-9 diagnoses, further analysis was only applied to patients with a single ICD-9 diagnosis.

The ICD-9 diagnoses (Table 1) were scattered over a broad range of categories; the three most frequent were: anxiety state (ICD-9 300.0)(30/91 = 33%), affective psychosis-endogenous depression (according to ICD Nr. 296.1, 296.3, 296.5)(25/91 = 28%), and depressive neurosis (ICD-9 300.4)(15/91 = 17%).

Further analysis was primarily based on comparison of these three subgroups.

2. *ICD-9 Diagnoses in Relation to Other Ways of Subtyping*

In DSM-III subtyping of panic attacks has been proposed according to the presence of agoraphobia, furthermore, it is required that panic attacks have a minimum frequency [13] within a fixed period (3 weeks) and that they are not due to other specified conditions. This manner of subtyping and ICD-9 classification were strongly associated (Table 2). Patients with affective psychosis (ICD-9) were mainly classified as panic disorder or were not classified as either DSM-III subgroup because panic attacks were due to MDE, patients with anxiety state (ICD-9) were mainly classified as panic disorder, patients with depressive neurosis (ICD-9) were mainly classified as agoraphobia with panic attacks.

According to SCID, panic disorder is present when at least 3 panic attacks have occurred within 3 weeks with at least one panic attack weekly; panic disorder is subclassified as panic disorder uncomplicated, with limited avoidance behavior, or with extensive avoidance behavior. No significant association between this manner of subclassification and the ICD-9 diagnoses was observed (Table 2).

Only a minority of patients were classified as anxiety or phobic neurosis according to Feighner Criteria; this was due to the extensive exclusion criteria and rigorous inclusion criteria for these diagnoses.

Subclassification according to Feighner Criteria was significantly associated with ICD-9 classification. Most patients classified as anxiety or phobic neurosis according to Feighner Criteria were classified as depressive neurosis or anxiety state by ICD-9 (Table 2).

According to the Anxiety-Depression-Discrimination Index, most patients were classified in the category of anxiety; this was mainly due to the high weighting score in favor of anxiety for panic attacks in this scale. In the group of patients with affective psychosis (ICD-9), the prevalence of the diagnoses "anxiety" according to Gurney et al. was lowest (Table 2).

Another manner of subtyping has been proposed [4, 20] according to the history or presence of MDE and its temporal relationship to the first manifestation of panic attacks; three subgroups can be formed:
subgroup PD: occurrence of an episode of MDE (DSM-III) after the first manifestation of panic attacks;
subgroup DP: occurrence of an episode of MDE prior to or contemporary with the first manifestation of panic attacks;
subgroup P: without any history or presence of MDE.

This subclassification was strongly associated with ICD-9 classification (Table 2). Patients with affective psychosis (ICD-9) were mainly classified as subgroup DP and vice versa, patients with depressive neurosis (ICD-9) were mainly classified as subgroup PD, and patients with anxiety state were

Table 3. Relationship between ICD-9 diagnosis and syndromes of anxiety and phobia

	Affective psychosis ($n = 25$)	Anxiety state ($n = 30$)	Neurotic depression ($n = 15$)
Mean number of panic attacks last week	4.6	4.0	4.2 N.S.
Mean number of panic attacks worst week	10.7	6.9	10.4 N.S.
Mean number of symptoms during panic attacks	7.4	9.9	8.2 **
Anticipated anxiety (% of time)	16.5	28.9	34.6 *
Mean age of onset of panic attacks	38.2	34.2	27.3 N.S.
Agoraphobia	3	14	10 **
Social phobia	9	12	10 N.S.
Simple phobia	12	15	10 N.S.
Obsessive–compulsive syndrome	11	6	11 **
Chronic anxiety	2	20	9 **

*, **: Significant difference (association) according to Kruskal-Wallis-χ^2 test ($P < 0.05, 0.01$)

Table 4. Relationship between ICD-9 diagnosis and depressive syndromes

	Affective psychosis ($n = 25$)	Anxiety state ($n = 30$)	Depressive neurosis ($n = 15$)
Present MDE	15	14	8 N.S.
Chronic depression	14	7	10 **
Number of previous episodes of MDE (present episode excluded)			
0	8	22	6
1– 4	10	5	6
5–10	7	3	3 *
Bipolar	7	0	0 **
Male	3	17	1
Female	22	13	14 **

*, **: Significant association according to χ^2 test ($P < 0.05, 0.01$)

Table 5. Characterization of the clusters resulting from empirical classification

Cluster 1 ($n = 25$) is characterized by:	
high frequency of history of or present primary depression	(20/25)
low frequency of agoraphobia	(2/25)
low frequency of obsessive–compulsive syndrome	(3/25)
low rate of chronic anxiety	(4/25)
late onset of panic attacks	(mean 37.6)
prevalence of female patients	(21/25)
high rate of hospitalization	(21/25)
relatively few symptoms during panic attacks (referring to DSM III panic attacks)	(mean 7.0)
Cluster 2 ($n = 24$) is characterized by:	
high frequency of a history of or present secondary depression	(20/24)
high frequency of agoraphobia	(21/24)
relatively high frequency of social phobia	(14/24)
relatively high frequency of obsessive–compulsive syndrome	(12/24)
relatively high rate of chronic anxiety	(14/24)
relatively high rate of chronic depression	(10/24)
Cluster 3 ($n = 21$) is characterized by:	
low frequency of a history of or present MDE	(1/21)
low rate of chronic depression	(2/21)
relatively low rate of chronic anxiety	(5/21)
relatively high rate of primary panic attacks	(10/21)
relatively low rate of hospitalization	(4/21)
relatively many symptoms during panic attacks referring to DSM-III panic attacks	(mean 10.5)

mainly classified as subgroup P but also with a substantial frequency as subgroup PD.

3. Characterization of subgroups defined by ICD-9 diagnosis by symptomatology

Patients with affective psychosis (ICD) differed significantly ($P < 0.05$, exact Fisher test, Kruskal-Wallis test, Bonferroni adjustment) from both other subgroups under study (defined by ICD-9 diagnosis of anxiety state and depressive neurosis – ICD-9) by (Tables 3, 4): low frequency of chronic anxiety, low frequency of agoraphobia, late onset of panic attacks, high frequency bipolar course of the affective disorder, high frequency of an episode of MDE primary to panic attacks, and high frequency of previous or present inpatient status.

Patients with the ICD-9 diagnosis of depressive neurosis differed significantly ($P < 0.05$, exact Fisher test, Kruskal-Wallis test, Bonferroni adjustment) from both other subgroups (defined by ICD-9 diagnoses of affective psychosis and anxiety state – ICD-9) by (Tables 3, 4): high frequency of symptoms during panic attacks (according to the set of 14 symptoms listed in SCID for panic attacks, early onset of panic attacks, high frequency of chronic depression, high frequency of an episode of MDE secondary to panic attacks.

Patients with the ICD-9 diagnosis of anxiety state differed significantly ($P < 0.05$ exact Fisher test, Kruskal-Wallis test, Bonferroni adjustment) from both other subgroups (defined by ICD-9 diagnosis of affective psychosis and depressive neurosis) by (Tables 3, 4): high frequency of male patients, low frequency of previous episodes of MDE.

Table 6. Empirical classification of panic attacks in relationship to prevailing ICD-9 diagnosis ($n = 91$)

ICD diagnosis/ Subtypes	Anxiety neurosis ($n = 30$)	Affective psychosis ($n = 25$)	Neurotic depression ($n = 15$)	Other ICD diagnoses ($n = 21$)
Empirical classification				
Cluster 1 ($n = 25$)	2	16	2	5
Cluster 2 ($n = 24$)	11	2	9	3
Cluster 3 ($n = 21$)	14	0	1	6
Not classified in either cluster ($n = 20$)	3	7	3	7

4. Empirical Classification

For assessing the utility of clusters of symptoms and associated features for justification of different diagnoses according to ICD-9, we established robust clusters by applying different statistical procedures. Variables included in the cluster analysis describe present and previous psychopathological features.

Three robust clusters were isolated, and 71% of patients (71/97) were classified in one of these stable clusters. The three stable clusters can be characterized by features associated with panic attacks (Table 5).

ICD-9 classification was associated with empirical classification (χ^2 test, $P < 0.01$): affective psychosis (ICD-9) overlapped considerably with cluster 1. Patients with neurotic depression (ICD-9) were predominately classified in cluster 2. Patients with anxiety state (ICD-9) scattered between clusters 2 and 3, and 30% of the cases were excluded from any stable cluster. Also in cluster 1 patients with anxiety state were significantly rare (Table 6).

Discussion

On the basis of the manner of selection, the sample presented can be considered as representative for treated patients with panic attacks. The ICD-9 diagnoses were scattered over a broad range. Secondary clinical diagnosis (ICD-9) for additional psychiatric features were not extensively used, additionally present syndromes, which can be considered to be due to the primary ICD-9 diagnosis, did not frequently give rise to a secondary ICD-9 diagnosis. Therefore, secondary ICD-9 diagnoses were rather rare in this sample. So no clear way for the identification of patients with panic attacks is included in ICD-9; this finding demonstrates the nonspecificity of panic attacks for the ICD-9 classification.

The three most frequent ICD-9 diagnoses in this sample were: anxiety state (ICD 300.0) ($n = 30$), affective psychosis-endogenous depression (ICD 296.1, 296.3) ($n = 25$), depressive neurosis (ICD 300.4) ($n = 15$); all other ICD-9 diagnoses showed a maximal frequency of $n = 6$. The prevalence of endogenous features (affective psychosis ICD-9) among patients with depressive disorders and panic attacks has been observed in other studies [4] using different diagnostic systems.

Patients with panic attacks who are diagnosed as affective psychosis-endogenous depression (ICD-9) were primarily characterized by a relatively high frequency of a history or presence of a primary MDE and mild features of anxiety (late first manifestation of panic attacks, low frequency of chronic anxiety). In these respects, this group differed from the subgroups of patients diagnosed as anxiety state and/or depressive neurosis equally. This finding demonstrates that ICD-9 diagnoses of affective psychosis indicate the primacy of depression relative to panic attacks, and the bipolar course of depressive episodes.

Female patients clearly predominated among patients diagnosed as affective psychosis-endogenous depression and among those diagnosed as neurotic depression; however, a slight predominance of male patients was observed among those diagnosed as anxiety neurosis. This finding was in contrast to epidemiological studies postulating a higher prevalence of females in anxiety and in depressive disorders in a German speaking general population [3]. It is beyond the scope of this paper to discuss hypotheses for the explanation of this finding (besides real sex differences in prevalence of anxiety state and depressive neurosis (ICD-9) in patients with panic attacks, there may be a sex-related bias in the report of symptoms or variations in the attitudes of diagnosticians related to the gender of patients).

Neurotic depression was associated with several additional present and previous syndromes (high frequency of chronic depression and of chronic anxiety, high frequency of secondary MDE following the manifestation of panic attacks). In these respects, this subgroup differed from affective psychosis and from anxiety state. But no difference in any variable between anxiety state and depressive neurosis (ICD-9) was so clear-cut that discrimination could be performed by one variable only.

Several ways of classification of patients with panic attacks are associated with the ICD-9 diagnoses (DSM-III, Feighner Criteria, Gurney Anxiety-Depression-Discrimination Index, subclassification according to the history of MDE). This can only partially be interpreted as a validation of the ICD classification. The associations were mainly due to the differences between patients with affective psychosis (ICD-9) on the one hand, and patients with depressive neurosis or anxiety state (ICD-9) on the other hand. However, between both neurotic disorders the differences were not prominent; therefore, the boundary between both neurotic disorders was not validated by these data.

Cluster analysis based on symptomatology is also a tool for the validation of classifications [6, 17]. To try to validate the different ICD-9 diagnoses, we performed a cluster analysis; subsequently, we compared the subgroups defined by ICD-9 diagnoses with those defined by cluster analysis. However, whereas patients in a particular cluster (cluster 1) were almost exclusively diagnosed as affective psychosis (ICD-9) and patients in another cluster (cluster 3) as anxiety neurosis (ICD-9), patients in the third cluster (cluster 2) were as a rule diagnosed either as anxiety state or depressive neurosis (ICD-9).

Thus, anxiety state (ICD-9) was scattered across cluster 2 and cluster 3 and did not describe a homogeneous cluster;

therefore, this diagnosis was compatible with a broad range in symptomatology and features of psychiatric history. Furthermore, due to the overlap in cluster 2, anxiety state (ICD-9) could not be discriminated from depressive neurosis by means of present symptomatology and previous syndromes consistently. On the other hand, the strong overlap between the ICD-9 classification of affective psychosis and cluster 1 may be considered as a validation of this particular ICD-9 diagnosis. These results are in accordance with another cluster analysis study reported by Everitt et al. [6]; he also tried to validate clinical diagnoses by cluster analysis and failed to find robust clusters corresponding to neurotic disorders.

The heterogenity of anxiety state (ICD-9) and the interference with depressive neurosis (ICD-9) observed in this study may be due to several reasons: (a) the diagnosis of anxiety state (ICD-9) and its discrimination from depressive neurosis (ICD-9) may be based on features not involved in this study (e.g., psychodynamic factors, psychosocial stress, subjective judgement of prevailing depressive or anxiety features); (b) though the diagnoses of anxiety state and depressive neurosis (ICD-9) were based on present and previous symptomatology, the diagnostic concepts varied among the diagnosticians involved in this study, a similar point being made for depressive neurosis by Klerman et al. [14].

Thus, the classification according to the diagnoses of neuroses (ICD-9) in the sample presented is not sufficient. The special way of selecting the sample under study did not allow us to make precise recommendations for better concepts of these disorders. Furthermore, because of the low reliability of ICD-9 diagnoses across different centers [9] the findings of this study can only cautiously be generalized. In spite of this, the attitudes of the diagnosticians towards patients with panic attacks in this study may reflect more general attitudes towards the three ICD-9 diagnoses which are most relevant in the sample presented (affective psychosis-endogenous depression, depressive neurosis, anxiety state). Thus, it can be concluded: (1) by the broad range of symptomatology corresponding to the ICD-9 diagnosis of anxiety state and the high degree of overlap with depressive neurosis (ICD-9) operational definitions of these disorders in the manual of ICD are recommended; relevant defining criteria may be the chronicity of anxiety and depression; (2) the missing possibility of identifying patients with panic attacks according to ICD-9 requires the supplementation of the ICD glossary by this disorder; the application of this diagnosis should be recommended when a minimum number of panic attacks has been reported. The identification of patients with prominent panic attacks and especially with panic attacks outside a depressive episodes is necessary, as special treatment with imipramine, alprazolam, or phenelzine is indicated in these cases.

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