MSA/NRS/98.1
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Distr.: Limited

PROGRAMME ON MENTAL HEALTH

IDENTIFICATION OF DYSTHYMIA IN NEUROLOGICAL DISORDERS

Report on the meeting of principal investigators involved in the field trial "Classification of Dysthymia and Related Conditions in Neurological Disorders"

DIVISION OF MENTAL HEALTH AND
PREVENTION OF SUBSTANCE ABUSE
WORLD HEALTH ORGANIZATION

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Report on the meeting of principal investigators involved in the field trial "Classification of Dysthymia and Related Conditions in Neurological Disorders"

This document arises from a WHO meeting held in Bethesda (USA) on 3-4 March 1998, of the principal investigators involved in the Classification of Dysthymia and Related Conditions in Neurological Disorders: Recommendation for the clinical descriptions and criteria for research: Version for field trials. The goal of the meeting was to discuss the results of the statistical analysis of the data collected during the phase of validation of the diagnostic checklist for dysthymia in neurological disorders.

UNIT OF NEUROSCIENCE
DIVISION OF MENTAL HEALTH AND
PREVENTION OF SUBSTANCE ABUSE
WORLD HEALTH ORGANIZATION
GENEVA

1998

This document is a report of the meeting of the principal investigators involved in the Classification of Dysthymia and Related Conditions in Neurological Disorders. The following experts participated:

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Dr Raoul DiPerri, University of Messina, Italy
Dr Julio Licinio, NIH, USA
Dr Pierre Ndiyae, Centre Hospitalo-Universitaire de Fann, Senegal
Dr Harold Pincus, Washington, D.C., USA
Dr Mary M. Robertson, University College, London, UK
Dr Robert G. Robinson, University of Iowa, USA
Dr Pierre Thomas, University of Lille II, France
Dr Shen Yucun (unable to attend), Beijing Medical University, People's Republic of China

WHO Secretariat

Dr C.L. Bolis, Consultant, Unit of Neuroscience, Division of Mental Health and Prevention of Substance Abuse (MSA)

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IDENTIFICATION OF DYSTHYMIA IN NEUROLOGICAL DISORDERS

1. INTRODUCTION

1.1 Opening

Dr Bolis opened the meeting and welcomed the participants to this WHO meeting of the Principal Investigators who have been involved in the Field Trial "Classification of Dysthymia and Related Conditions in Neurological Disorders: Recommendations for the Clinical Descriptions and Criteria for Research." The agenda of the meeting was discussed and approved. Dr Julio Licinio was appointed as chairman, Dr Raoul DiPerri as vice-chairman, and Drs John Bartko and Robert Robinson as rapporteurs.

1.2 Previous activities of WHO in this field

Dysthymia is an important and clinically relevant diagnosis in patients with neurological disorders. The study group had agreed that in neurological disorders dysthymia is important, but under-recognized and under-investigated. Because neurological disorders, in many cases directly affect the brain, it is reasonable to propose a biological basis for dysthymia in some cases. Moreover, some neurological disorders have abrupt onset and defined neuroanatomical basis. In those cases, particularly, it is not very useful to wait two years for the diagnosis of dysthymia to be made. The symptoms of hopelessness, fearfulness, inability to cope with problems of daily living, and persistent pessimism, which are characteristic of dysthymia, are also common in patients with neurological disorders.

The work done by WHO in dysthymia since July 1996 that resulted in the publication of (1) a WHO meeting report entitled "Dysthymia in Neurological Disorders"; (2) a WHO book entitled "Dysthymia in Neurological Disorders "; (3) a WHO book entitled "Dysthymia: From Clinical Neuroscience to Treatment"; and (4) a peer-reviewed article entitled "Dysthymia in Neurological Disorders" [***Molecular Psychiatry*** 1996; 1: 478-491]. Additionally, WHO developed the "Classification of Dysthymia and Related Conditions in Neurological Disorders: Recommendations for the Clinical Descriptions and Criteria for Research: Version for Field Trials."

In the previous WHO meeting in Geneva, July 1-3, 1996, it was agreed that dysthymia is complementary to Parkinson's disease, Alzheimer's disease, Tourette's syndrome, stroke, multiple sclerosis, and epilepsy. It was also agreed that further studies were needed to clarify

the etiology, biology, clinical manifestations, and treatment of dysthymia in neurological disorders. For this reason WHO prepared a "Classification of Dysthymia and Related Conditions in Neurological Disorders: Recommendations for the Clinical Descriptions and Criteria for Research" to be used in field trials. That instrument included a diagnostic checklist for dysthymia in neurological disorders which was applied in selected participant centers: France, Italy, People's Republic of China, Senegal, UK, and USA. In the present meeting these results were discussed.

1.3 Scope of the meeting

Dr Bolis stressed the purposes of the meeting as follows:

- to evaluate the validity of the proposed Classification of Dysthymia and Related Conditions in Neurological Disorders: Recommendations for the Clinical Descriptions and Criteria for Research by selected centers worldwide;

- discuss the results of the statistical analysis of the diagnostic checklist for dysthymia in neurological disorders; and

- finalize the text of the publication.

2. RESULTS OF THE STUDIES

2.1 Results of the neuroendocrine study

Dr Licinio presented the results of his ongoing endocrine studies on patients with "atypical" mood symptoms that include overeating, oversleeping, fatigue, and lethargy. Those are shared by patients with "atypical depression", dysthymia, and chronic fatigue. The variables studied were plasma levels of adrenocorticotropic hormone (ACTH) and cortisol. The results showed clear differences in the level of organization of neuroendocrine function in classical melancholic depression and in "atypical" syndromes. In 22600 hormone samples measured, he found that ACTH levels were reduced in atypical states (19.2±0.4 pg/ml in controls and 10.4±0.2 in atypical patients, $P < 0.05$); however, cortisol levels were unchanged (8.4±0.2 and 7.8±0.2, non-significant). These data indicate that ACTH is a better marker of endocrine dysfunction in these patients than cortisol. The work is now ongoing to further characterize neuroendocrine function in dysthymia.

2.2 Results of statistical analysis of clinical data obtained

Those centers, which interviewed approximately 450 patients, are at the University of Messina, Italy; Centre Hospitalo-Universitaire de Fann, Senegal; University College London, UK;

University of Iowa, USA; University of Lille II, France; Beijing Medical University, People's Republic of China; and the Clinical Neuroendocrinology Branch, NIMH, NIH.

Dr John Bartko, statistical editor of the *American Journal of Psychiatry*, conducted a detailed statistical analysis of each symptom by duration of dysthymia. The statistical analysis was conducted as follows:

Contingency table (cross tabulations, chi square statistics) analyses were performed comparing the duration variable, [the duration variable following item 7] in the diagnostic checklist with the other variables in the checklist. Note that item numbers refer to items as listed in the checklist (for details of method see Altman & Douglas 1991).

The duration variable is coded 0, 1 and 2, where

0 = From 1 to 6 months
1 = From 6 months to 2 years and
2 = At least 2 years.

The total number of subjects across the eight sites, in the data base is 256. The eight sites are Iowa (N = 25), France (N=30), Italy (N=97), Senegal (N=8), China (N=16), Senegal B (N=62), France B (N =12) and England (N=6). See Table 1.

Table 1. Cross Tabulation Report

Counts Section

Duration (Following item 7 in the Check List)

Site code	Not Used	0	1	2	Total
Iowa	25	0	0	0	25
France	0	6	18	18	42
Italy	69	5	11	12	97
Senegal	64	6	0	0	70
China	2	5	0	9	16
England	4	0	0	2	6
Total	164	22	29	41	256

The number of subjects with coded Duration values is 256 - 164 = 92.

As Table 1 illustrates, not all of the 256 subjects received a duration code. The table is arranged, site by duration, since duration is the cross tabulation variable against which others will be assessed. The number of usable duration values or subjects is 256 - 164 = 92. Of these 92 durable scores, 22 were coded 0, 29 coded 1 and 41 coded 2.

Chi Square Statistics

The Chi square statistic for cross tabulation tables (Altman, 1991) assess the association between a categorical row and a categorical column variable. The rows and columns are partitioned into their respective levels of response. The entries in the cells of the tables are counts.

As an aid to appreciating and understanding the chi square statistic, two hypothetical examples follow. These examples illustrate the statistic's two extreme ranges. The first example illustrates perfect association and a maximum chi square statistic.

A perfect association table could have the (hypothetical data example) format of:

Example 1

		Column Variable			
		Category A	Category B	Category C	Total
Row Variable	Category 0	30	0	0	30
	Category 1	0	30	0	30
	Category 2	0	0	30	30

The Chi square statistic for this example is as large as it could possibly be. Its value is, Chi square =180, df = 4, $p < 0.000001$. A *p* value of this size, conveys the notion of a pronounced statistical significance. This chi square statistic suggests a strong association between the row and column variables as opposed to no association. This is evident by inspection. We see that 100% of the first row is associated with the first column; 100% of the second row is associated with the second column and 100% of the third row is associated with the third column. For a given row, the predicted response for the column is known exactly. Likewise for a given column, the predicted or associated response for the row is known exactly. The association is perfect. The chi square statistic is large, suggesting non independence and strong association. The small *p* value supports this notion.

The next example represents the lower extreme, that is where there is absolutely no association between the row and the column variables.

Example 2

		Column Variable			
		Category A	Category B	Category C	Total
Row Variable	Category 0	10	10	10	30
	Category 1	10	10	10	30
	Category 2	10	10	10	30

The Chi square statistic for this example is as small as possible and that is zero. Chi square = 0, df = 4, p =1.0. This chi square statistic indicates, and the table demonstrates, that there is absolutely no association between the row and column variables. The rows are evenly or uniformly spread (1/3, 1/3, 1/3) across the columns. There is no association between a row Category and a column Category. Rows and columns are said to be independent.

Presented next are the chi square results for the actual dysthymia checklist variables where each is assessed against the duration variable.

Chi Square Analysis for the Dysthymia Variables

Chi Square cross tabulation statistics were performed for duration vs. the following variables. Recall that duration is coded as follows: Code 0: 1 to 6 months. Code 1: 6 months to 2 years and Code 2 at least 2 years. This duration variable follows item 7 in the checklist.

Example 3

Checklist Variable	Chi Square Statistic	df	p value
1	3.23	2	0.20
2.a.1	2.94	6	0.82
2.a.2	6.60	6	0.36
2.a.3	2.79	6	0.83
2.a.4	5.16	6	0.52
2.b.1	4.09	6	0.66
2.b.2	1.65	2	0.44
2.c.1	3.60	4	0.46
2.c.2	1.34	6	0.97
2.c.3	2.40	6	0.88
2.c.4	3.73	6	0.71
2.c.5	6.18	6	0.40

Example 3 (Continued)

Checklist Variable	Chi Square Statistic	df	p value
2.c.6	8.35	4	0.08
2.c.7	10.05	6	0.12
3.a.1	6.40	6	0.38
3.a.2	3.20	6	0.78
3.a.3	0.30	2	0.86
3.a.4	1.91	2	0.38
3.a.5	5.83	6	0.44
3.b.1	4.32	6	0.63
3.b.2	3.04	6	0.80
3.b.3	5.29	4	0.26
3.b.4	0.87	4	0.92
3.b.5	8.66	6	0.19
4	1.73	4	0.78
Duration_1	105.90	4	0.0000
See Tables 2 & 3			
5.a	1.76	4	0.78
5.b	6.70	6	0.35
5.c	3.00	6	0.81
5.d	8.05	6	0.23
5.e	2.44	4	0.65
6.a	3.17	2	0.20
6.b	No Statistics Possible.	All responses a "No".	
6.c	1.23	2	0.54
6.d	No Statistics Possible.	All responses a "No".	
6.e	No Statistics Possible.	All responses a "No".	
6.f	No Statistics Possible.	All responses a "No".	
7 absent	3.17	2	0.20
7 present	3.17	2	0.20

There was only one statistically significant chi square association, which was that of duration (following item 7 in the checklist) by Duration_1 (following item 4 in the checklist); this represents an association of duration of neurological disorder and duration of dysthymia. Thus, in the presence of neurological disorders, dysthymia was not a pre-existing condition, and had its onset at the time of onset of neurological disorder. There were no significant chi square associations between duration of dysthymia and specific symptoms of dysthymia. This demonstrates that the symptoms of dysthymia were the same irrespective of the duration of the dysthymia; thus, duration of illness does not seem to affect the clinical picture of dysthymia in neurological disorders.

Tables 2 and 3 present the full data for the statistically significant Chi Square, Duration by Duration_1. The data and statistics in these two tables are identical. The difference is in the frame of reference, that is which of the two duration variables is used as the benchmark.

Table 2. Cross Tabulation Report

Duration_1 follows item 4 in the check list. Duration follows item 7 in the check list.

Counts Section

	Duration_1			
Duration	**0**	**1**	**2**	**Total**
0	16	3	2	21
1	0	20	7	27
2	0	2	39	41
Total	16	25	48	89

Column Percentages Section

	Duration_1			
Duration	**0**	**1**	**2**	**Total**
0	100.0	12.0	4.2	23.6
1	0.0	80.0	14.6	30.3
2	0.0	8.0	81.3	46.1
Total	100.0	100.0	100.0	100.0

Chi-Square Statistics Section

Chi-Square	105.926501	
Degrees of Freedom	4.000000	
Probability Level	0.000000	Reject Ho
Kendall's tau-B (with correction for ties)	0.795077	
Kappa reliability test	0.747875	
Kappa's standard error	0.076293	
Kappa's t value	9.802651	
Kappa p value	0.00001	

Table 3. Cross Tabulation Report

Duration_1 follows item 4 in the check list. Duration follows item 7 in the check list.

Counts Section

	Duration			
Duration_1	**0**	**1**	**2**	**Total**
0	16	0	0	16
1	3	20	2	25
2	2	7	39	48
Total	21	27	41	89

Column Percentages Section

	Duration			
Duration_1	**0**	**1**	**2**	**Total**
0	76.2	0.0	0.0	18.0
1	14.3	74.1	4.9	28.1
2	9.5	25.9	95.1	53.9
Total	100.0	100.0	100.0	100.0

Chi-Square Statistics Section

Chi-Square	105.926501	
Degrees of Freedom	4.000000	
Probability Level	0.000000	Reject Ho
Kendall's tau-B (with correction for ties)	0.795077	
Kappa reliability test	0.747875	
Kappa's standard error	0.076293	
Kappa's t value	9.802651	
Kappa p value	0.00001	

For example, in Table 2, the frame of reference is Duration_1 (the duration variable following item 4 in the checklist). The column percentage section illustrates that of the 16 Duration_1 values coded 0 (recall that 0 is from 1 to 6 months), 100% of these 16 of 16 were coded 0 for Duration (the duration variable following item 7 in the checklist). For the 25 Duration_1 values coded 1 (from 6 months to 2 years), 12% (3/25) were coded Duration 0, 80% (20/25) were coded Duration 1 and 8% (2/25) were coded Duration 2. For the 48 Duration_1 values coded 2 (at least 2 years), 4.2% (2/48) were coded Duration 0, 14.6% (7/48) were coded Duration 1 and 81.3% (39/48) were coded Duration 2.

These column percentages also appear in the graph section of Table 2. For Duration_1 Coded 0, the open circle plot is 100% for Duration 0, 0% for Duration 1 and 0% for Duration 2. Similarly for the other two coded responses for Duration_1.

Table 3 is identical to Table 2, however, the frame of reference is Duration (the duration variable following item 7 in the checklist). The column percentage section illustrates that of the 21 Duration values coded 0 (recall that 0 is from 1 to 6 months), 76.2% of these (16/21) were coded 0 for Duration_1 (the duration variable following item 4 in the checklist), 14.3% (3/21) were coded 1 for Duration_1 and 9.5% (2/21) were coded 2 for Duration_1 . For the 27 Duration values coded 1 (from 6 months to 2 years), 0% (0/27) were coded 0 for Duration_1, 74.1% (20/27) were coded 1 for Duration_1 and 25.9% (7/27) were coded 2 for Duration_1. For the 41 Duration values coded 2 (at least 2 years), 0% (0/41) were coded 0 for Duration_1, 4.9% (2/41) were coded 1 for Duration_ 1 and 95.1% (39/41) were coded 2 for Duration_1.

These column percentages also appear in the graph section of Table 3. For Duration Coded 1, the triangle plot displays the 0% for code 0 at Duration_1, 74.1% for code 1 at Duration_1 and 25.9% for code 2 at Duration_1. Note that the plot of Duration code 1 has the shape of an upside down "V".

The large Chi Square value in these identical tables illustrates the strong association between Duration and Duration_1. Kendall's tau, a measure of association is about 0.8. A perfect associated value is unity. Kappa is a measure of agreement between the two duration variables. Kappa is 0.75 with a p value < 0.0001. Perfect kappa association is unity.

2.3 Summary of statistical analysis

First, a chi-square analysis of the data showed that there was a highly significant relationship between onset of neurological disorder, and onset of dysthymia (chi-square: 114.91; df: 4.0; $P < 0.000001$). Only 7 patients out of 89 had a dysthymic disorder which preceded the neurological disorder (see table 1). In other words, dysthymia was *not* a chronic condition that pre-existed the neurological disease, but it was rather a condition that came about at the time of onset of neurological illness. A careful analysis of the effects of duration of dysthymia on the features of each symptom of that disorder showed that there was no relationship between duration

of dysthymia and the other symptoms of dysthymia. Thus, the clinical syndrome presented by patients meeting the criteria for dysthymia was essentially the same, irrespective of the duration of dysthymia. In conclusion, in the context of neurological disorders, it does not seem to be appropriate to wait two years for a diagnosis of dysthymia to be made.

The protocol that was utilized seems appropriate for field trials, with an acceptable intra-instrument reliability (kappa reliability test of 0.74). It was agreed by the participants that an article with these results should be prepared for publication in a peer-reviewed scientific journal.

3. CONCLUSIONS AND RECOMMENDATIONS

Based on the data presented and discussed, it was concluded that in neurological disorders dysthymia was not a chronic condition that pre-existed the neurological disease, but it was rather a condition that came about at the time of onset of neurological illness. Moreover, the clinical syndrome presented by patients meeting the criteria for dysthymia in neurological disorders was not affected by the duration of dysthymia. Therefore, in the context of neurological disorders, it does not seem to be appropriate to wait two years for a diagnosis of dysthymia to be made.

After a discussion of the terminology, it was agreed that the term dysthymia should be maintained to correspond to the work done by this group since 1996 and it seems that the term dysthymia is adequate to refer to the symptoms that have been studied in patients with neurological disorders.

It was agreed by all the participants that this work should be continued and that training programmes should be instituted in various countries so that practitioners can identify and treat patients with dysthymia in neurological disorders.

Dr Robert Robinson suggested that the title of this report should be "Identification of Dysthymia in Neurological Disorders." This recommendation was unanimously approved by all participants, because it accurately reflects the data reported.

Based on the current study results, some recommendations have been made to include additional information to the protocol for future studies:

1. A supplementary information with limited additional demographic and historical information could be included in the checklist (see Annex 2).

2. The age of onset should be amended to "age of onset of neurological disorder."

3. The exclusion criteria for major depression ought to be clarified.

4. The titles of items 4 should be re-phrased to further emphasize that 4.a refers to duration of ***neurological disorder*** and that 4.6 represents ***exclusion criteria.***

5. The checklist should be translated into French for use in Francophone countries, including those of West Africa.

Dr Harold Pincus, Director, Office of Research, American Psychiatric Association attended the meeting on March 4, 1998. He was informed of the work to date, and found the proposed classification of dysthymia in 3 categories, based on duration, interesting and asked to be kept informed of the progress in this line of work. Dr Pincus said that the use of the term "dysthymia" by the group seemed appropriate and that it is important for this work to continue.

4. REFERENCE

Altman, Douglas G. Chi Square. The general case for the r x c table. *Practical Statistics for Medical Research.* Chapman and Hall: New York, 1991. pp. 242-249.

ANNEX 1

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ANNEX 2

SUPPLEMENTARY INFORMATION

1. Medication use

	for dysthymia	for neurological disorder
past		
present		

2. Presence of stressful life events
(including the onset of neurological disorder)
List in chronological order:

3. Presence of localized brain lesion
No _____
Yes, specify region: _____

4. Neurological disorder onset:
Abrupt onset _____
Chronic/slow onset _____

5. Previous personal history of substance abuse (drugs/alcohol)
No _____
Yes, specify _____

6. Presence of other medical, neurological or psychiatric diagnoses, with dates of onset: