Dysthymia in neurological disorders

Proceedings of the WHO Meeting

Editors: J. Licinio, L. Prillipko, C.L. Bolis

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Dysthymia in Neurological Disorders: 
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Preface

Long-lasting periods of decreased mood are frequently present in patients with neurological disorders. On 1-3 July 1996 the World Health Organization meeting “Dysthymia in Neurological Disorders” addressed this topic. Experts from all continents presented new research data on dysthymia in neurological disorders and discussed issues related to classification, definition, epidemiology, clinical manifestations, biological mechanisms, and treatment. A consensus emerged that the presence of dysthymia in the context of neurological disorders is a newly emerging area of interest to clinicians and investigators alike. Given the high prevalence of neurological disorders and the considerable interface between dysthymia and neurological disorders, this represents a substantial public health problem worldwide. This area is still under-recognized, and patients who suffer from both dysthymia and neurological disorders are therefore under-diagnosed and under-treated. We believe that by disseminating the latest research from centers of excellence worldwide awareness of this important area will increase and further research will be stimulated. A summary of the meeting was published in Molecular Psychiatry (1997; 1:478-491) and also as a separate WHO publication. In this volume we present the full text of all the papers presented in Geneva on 1-3 July 1996. We thank Radrel Lisman and Paulo J. Negro for their assistance volume.

The papers in this volume cover different aspects of dysthymia, including clinical aspects, biological mechanisms, and treatment. The term dysthymia has its origins in antiquity. For centuries, it has been recognized in the medical as well as in the lay literature that some individuals have chronic, long standing, low grade alteration in mood. The presentation of these individuals had been conceptualized as temperament or “depressive personality”. It has only been in the last few decades that a novel concept has been created to address such patients. Rather than view them as having a constitutional, personality-related low grade decrease in mood and persistent pessimism, we now think of such a clinical presentation as a disorder, dysthymia, that can be of particular relevance in the context of neurological disorders. Conceptualizing dysthymia in neurological disorders as a specific disorder, rather than a personality structure or just a reaction to being ill, makes it possible for investigators to use diagnostic instruments to assess clinical presentation in a structured way, and to collect systematic information on epidemiological aspects, clinical features, biological mechanisms, course, outcome, prognosis, and response to treatment. Such systematically collected data will be of benefit not only to those working in the field, but ultimately to patients, and to their families.

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# Table of Contents

**Preface**

<table>
<thead>
<tr>
<th>Chapter 1. The Concept and Classification of Dysthymia</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Abstract</td>
<td>1</td>
</tr>
<tr>
<td>1.2 Keywords</td>
<td>1</td>
</tr>
<tr>
<td>1.3 Introduction</td>
<td>1</td>
</tr>
<tr>
<td>1.4 Basic problems of classification</td>
<td>2</td>
</tr>
<tr>
<td>1.4.1 Dualistic Perspectives</td>
<td>2</td>
</tr>
<tr>
<td>1.4.2 Symptoms as Diagnostic Criteria</td>
<td>3</td>
</tr>
<tr>
<td>1.4.3 The Boundaries between Depressive Disorders</td>
<td>3</td>
</tr>
<tr>
<td>1.4.4 Comorbidity and Diagnostic Stability</td>
<td>4</td>
</tr>
<tr>
<td>1.4.5 The Spectrum of Mood Disorders</td>
<td>4</td>
</tr>
<tr>
<td>1.4.6 Coping and Adjustment</td>
<td>4</td>
</tr>
<tr>
<td>1.4.7 Treatment Outcome</td>
<td>5</td>
</tr>
<tr>
<td>1.5 Basic Differences between ICD-10 and DSM-IV</td>
<td>5</td>
</tr>
<tr>
<td>1.6 Particular differences regarding Dysthymia</td>
<td>6</td>
</tr>
<tr>
<td>1.6.1 Major Depressive Episode/Depressive Episodes</td>
<td>6</td>
</tr>
<tr>
<td>1.6.2 Cyclothymic Disorders</td>
<td>7</td>
</tr>
<tr>
<td>1.6.3 Secondary Depression</td>
<td>7</td>
</tr>
<tr>
<td>1.6.4 Recurrent Depressive Disorder</td>
<td>7</td>
</tr>
<tr>
<td>1.6.5 Adjustment and Stress Disorders</td>
<td>7</td>
</tr>
<tr>
<td>1.6.6 Other Anxiety Disorders</td>
<td>8</td>
</tr>
<tr>
<td>1.6.7 Mixed Anxiety Depressive Disorders</td>
<td>8</td>
</tr>
<tr>
<td>1.6.8 Neurasthenia</td>
<td>8</td>
</tr>
<tr>
<td>1.6.9 Panic Disorder</td>
<td>9</td>
</tr>
<tr>
<td>1.6.10 Depression in Primary Care</td>
<td>9</td>
</tr>
<tr>
<td>1.6.11 Personality Disorders and Characterological Problems</td>
<td>9</td>
</tr>
<tr>
<td>1.7 Conclusion</td>
<td>10</td>
</tr>
<tr>
<td>1.8 References</td>
<td>11</td>
</tr>
</tbody>
</table>

**Chapter 2. Clinical Epidemiology of Dysthymia in the Western World**

| 2.1 Toward a Clinical Classification of Dysthymia     | 13   |
| 2.2 Antecedents of Dysthymia in Western Medicine and Psychiatry | 14   |
| 2.3 Contemporaneous Validation of Dysthymia as a Form of Affective Pathology | 15   |
| 2.4 Dysthymia and Medical-Neurologic Disease          | 16   |
| 2.5 Concluding Remarks                                | 17   |
| 2.6 References                                        | 18   |
Chapter 3. Dysthymia in Children

3.1 Introduction
3.2 Prevalence of Dysthymia in Children
3.3 Risk Factors of Dysthymia in Children
3.4 Biological Basis of Dysthymia in Children
3.5 Clinical Characteristics
3.6 Treatment and Prognosis
3.7 References

Chapter 4. Epidemiology of Dysthymia in South America

4.1 References

Chapter 5. The Neuroendocrinology of Dysthymia

5.1 Documentation of Hypercortisolism in Depression
5.2 Discovery of CRH
5.3 CRH in Major Depression
5.4 Thyroid Hormone Alterations
5.5 Research in the Neuroendocrinology of Dysthymia
5.6 Evidence for decrease HPA Activity in Subtypes of Affective Disorder: implications for Dysthymia
5.7 Concluding Remarks
5.8 References

Chapter 6. Molecular Mechanisms of the Stress Response and their Role in the Pathogenesis of Dysthymia

6.1 Abstract
6.2 Are Mood Disorders Stress-Related Disorders?
6.3 The Molecular Basis of the Stress Response
6.4 Corticotropin-Releasing Hormone
6.5 Proopiomelanocortin Corticotropin-Releasing Hormone Responsive Element Binding Protein 1 (PCRH-REB-1)
6.6 Concluding Remarks
6.7 References

Chapter 7. The Role of Dopamine in the Biological Basis of Dysthymia

7.1 Abstract
7.2 Introduction
7.2.1 Dopamine, Desire, Drive, Pleasure
7.2.2 Intracranial self-stimulation
7.2.3 Self-Administration of Drugs
7.3 Natural Stimuli
7.3.1 Sexual Behavior
7.3.2 Food and Sweets
7.4 Depression after Withdrawal from Chronic Psychostimulants
7.5 Animal Models of Depression
7.6 Mesolimbic DA and Antidepressants
7.6.1 Antidepressant Treatments and DA
7.7 Clinical Considerations
7.8 References

Chapter 8. Cerebral Blood Flow in Dysthymia
8.1 Brain Imaging Studies in Primary Major Depression
8.2 Brain Imaging Studies in Secondary Depression
8.3 Brain Imaging Studies in Dysthymia
8.4 References

Chapter 9. Dysthymia in Patients with Stroke and Neurological Disorders
9.1 Introduction
9.1.1 Prevalence
9.1.2 Clinical Correlates of Post-Stroke Dysthymia
9.1.3 Treatment of Post-Stroke Dysthymia
9.2 Conclusions
9.3 References

Chapter 10. Dysthymia in Parkinson's Disease
10.1 Prevalence
10.2 The Course of Depression in Parkinson's Disease
10.3 Correlates of Depression in PD
10.4 Mechanism of Dysthymia in PD
10.5 Treatment of Depression in PD
10.6 Acknowledgments
10.7 References
Chapter 11. Dysthymia in Alzheimer’s Disease

11.1 Prevalence
11.2 Correlates of Depression in AD
11.3 Mechanism of Depression in AD
11.4 Treatment of Depression in AD
11.5 Acknowledgments
11.6 References

Chapter 12. Dysthymia in Multiple Sclerosis

12.1 Introduction
12.2 Depression in MS
12.3 Suicide
12.4 Research Study: Dysthymia in MS
  12.4.1 Suicide, Attempted Suicide, Suicidal Plans
12.5 Discussion
12.6 References

Chapter 13. Dysthymia in Epilepsy

13.1 Introduction
13.2 Dysthymia
13.3 Dysthymia in PWE
13.4 Depression in PWE
13.5 Prevalence
13.6 Characteristics of Depression in PWE
13.7 Aetiology of Depression in PWE
  13.7.1 Genetic Vulnerability
  13.7.2 Gender
  13.7.3 Psychosocial Factors
  13.7.4 Neuroepilepsy Variables
  13.7.5 Possible Aetiological Factors of Dysthymia in PWE
  13.7.6 Management
13.8 Conclusions and Directions for Future Research
13.9 References

Chapter 14. Dysthymia and Epilepsy in Developing Countries

14.1 Introduction
14.2 Patients and Methods
## Chapter 15. Psychological Treatment of Dysthymia

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.1 Features of Dysthymia and Psychotherapy</td>
<td>114</td>
</tr>
<tr>
<td>15.2 Psychotherapy Goals and the Psychotherapeutic Process in Dysthymia</td>
<td>115</td>
</tr>
<tr>
<td>15.3 Clinical Studies on the Effectiveness of Psychotherapy in Dysthymia</td>
<td>118</td>
</tr>
<tr>
<td>15.4 Conclusions and Recommendations</td>
<td>119</td>
</tr>
<tr>
<td>15.5 References</td>
<td>120</td>
</tr>
</tbody>
</table>

## Chapter 16. Pharmacotherapy of Dysthymia

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.1 Introduction</td>
<td>124</td>
</tr>
<tr>
<td>16.2 Open Trials Conducted in Chronic Minor, Intermittent Depression</td>
<td>124</td>
</tr>
<tr>
<td>or Dysthymic Patients (DSM)</td>
<td></td>
</tr>
<tr>
<td>16.3 Double Blind Comparisons Conducted with MAOIs in Chronic Minor</td>
<td>125</td>
</tr>
<tr>
<td>or Intermittent Depression likely to Include Dysthymic Patients</td>
<td></td>
</tr>
<tr>
<td>16.4 Double Blind Comparisons Conducted in Patients with Dysthymia</td>
<td>126</td>
</tr>
<tr>
<td>16.5 Double Blind Comparisons Conducted in Pure Dysthymic Patients</td>
<td>127</td>
</tr>
<tr>
<td>16.6 Stability of Remission in Dysthymic Responders</td>
<td>128</td>
</tr>
<tr>
<td>16.7 Conclusion</td>
<td>129</td>
</tr>
<tr>
<td>16.8 References</td>
<td>130</td>
</tr>
</tbody>
</table>
THE CONCEPT AND CLASSIFICATION OFDYSTHYMIA

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ABSTRACT

Since DSM-III (APA, 1980) the category of dysthymia includes patients that in the past have been considered as neurotic, reactive, characterological, temperamental, minor or atypical depressives as opposed to a category of endogenous, autonomous, morbid, major or typical depressives. In spite of certain confusion, the need of a nosological category for patients who suffer the burden of years long depressive mood, with a significant impact on their life-styles and adaptation, is very important as they can benefit from antidepressant treatments.

DSM-IV (APA, 1994) and ICD-10 (WHO, 1992) describe dysthymia in a very similar way although there are significant differences. Some reflect decisions taken when lacking of sufficient scientific data and its analysis allows to pinpoint areas for future research. Other differences are the consequence of major discrepancies in basic perspectives of the classifications (i.e. in the importance given to handicap for the diagnosis). The similarities between both classifications allow the use of any of them for most of the purposes. Research on the differences should allow a progress in defining the concept of dysthymia and mood disorders in general (i.e., the cut-off points between them) and of psychiatric nosology.

KEYWORD: Dysthymic disorder, depressive disorders, personality disorders, ICD-10, DSM-IV.

INTRODUCTION

Chronic depressive conditions of a relatively mild nature, have been known for centuries, but they were interpreted as the consequence of long lasting negative life conditions, of childhood developmental failures, of persistent characterological problems or to a combination of the three. Therefore, the clinical manifestations, the symptoms, lost relevance in face of the pathogenetic factors, and they were considered just a secondary or even as a mask of those factors.
DSM-III (APA, 1980) changed this approach and dysthymic disorder is a totally new concept, which in spite of its importance it is often criticized, specially in some European countries where the endogenous-reactive distinction was widely accepted and where words of a common Greek legacy may have different meanings (dysthymia, in German, Verstimmung, is used for unspecific alterations of mood or for an irritable mood, of a duration as long as any mood state can last).

The chronic character of the dysthymic disorder also lead to misunderstanding, and for many European psychiatrists, dysthymic disorder was a category corresponding more to depressive personality than to neurotic depression. This is reinforced by the fact that depressive personality disappeared from DSM-III and that it is one of the inclusion terms for dysthymia in ICD-10 (WHO, 1992). Its reemergence in DSM-IV (APA, 1994) appendix will add bewilderment to many practicing clinicians, until proper diagnostic criteria and tools are developed for the identification of this disorder.

Mood disorders are the more complicated to classify of all psychiatric disorders and it is difficult to find an acceptable definition of what a mood disorder is. DSM-III used the words affective disorders, while DSM-III-r and ICD-10 preferred the expression mood (affective) disorders and DSM-IV, indeed very correctly, just mood disorders. Many different criteria are used to classify them, including clinical manifestations of the episode, severity, chronicity, recurrence, and the presence of specific symptoms constellation such as melancholia (somatic symptoms in ICD-10) or psychotic features.

Reliability studies show in general lower kappa values for mood (affective) disorders than for most of other psychiatric disorders excluding personality disorders and, but not always, neurotic and anxiety disorders. The results from ICD-10 provisional version field trials (Sartorius et al., 1993) are shown in table I. As a contrast, clinician ratings which evaluate the goodness of fit, the confidence in classification, the easiness and the level of adequacy of the classification are comparatively much better although the scores are particularly low for dysthymia. When comparing ICD-10 with DSM-III-r (Mellisop et al., 1991) the figures for reliability for ICD-10 are higher than those for DSM-III-r and comparable between the ICD-10 Clinical Description and Diagnostic Guidelines and the Diagnostic Criteria for Research versions although in this study the number of cases was relatively small.

**BASIC PROBLEMS OF CLASSIFICATION**

*Dualistic Perspectives*

The trend to subdivide disorders characterized by the presence of a depressive mood has been present for centuries. Teresa de Jesús (1643), the Spanish reformer of the Carmelitan order in the 16th century insisted that an early distinction between melancholia as a disease and the melancholic character should be made in order to take adequate decisions in the convents, i.e. to provide compassionate care to patients while trying to identify characterological problems early enough to prevent the negative impact on the life of a religious community that they have.

This dualistic view has often been challenged. For Andrés Piquer, who in the 18th century treated Ferdinand the VI for his melancholia, some characterological traits – present before his melancholia – were already manifestations of the disease of the Spanish King and not of his melancholic temperament (López-Ibor Jr., 1982).
During the present century several English authors put forward a unified perspective of depressive disorders and described that the dichotomy was well accepted because it justified treatment decisions (Kendell, 1968). Other factors playing a role in the distinction were: severity of the symptoms, reactivity to external influences (autonomy, Gillespie, 1929), acute manifestations vs. chronic evolution, spontaneous recovery vs. stable course. Along this line, clinical and psychopathological research led López-Ibor (1950, 1966) to recognize endogenous elements in neurotic disorders, not only in neurotic depression, and paved the way for biological treatments in this field.

**Symptoms as Diagnostic Criteria**

DSM-III reintroduced in psychiatry a classification system based on the symptoms and clinical manifestations. Psychiatric disorders are defined by the presence or the absence of certain symptoms. The risk of the “Chinese restaurant menu”, in which with the same dishes different guests can self-tailor different menus is avoided with sets of rules which define the number and type of symptoms which allow cut-off points with normality and with other disorders.

Such an approach has to solve two practical problems when a patient fulfills to few criteria or when he or she fulfills criteria for more than one disorder. In the first case the diagnosis falls into one of the residual or atypical categories. In the second case DSM-III adopted the traditional approach of a hierarchy of diagnosis, based on exclusion criteria. But as a nosological hierarchy is often based on theories or assumptions lacking scientific evidence and not always solved by consensus, DSM-III-r and ICD-10 and DSM-IV became less hierarchical. This allows a patient to get more than one diagnosis when he or she fulfills criteria for several entities. Several diagnosis doesn’t mean several distinct diseases (Francés et al., 1990).

**The Boundaries between Depressive Disorders**

Akiskal and Weise (1992) and Angst (1992) have criticized the present concept and boundaries of major depression, dysthymia and recurrent brief depression and have proposed a spectrum model while Hirschfeld (1994) simply criticizes the differentiations. The existing data does not provide convincing evidence that major depression, dysthymia and recurrent brief depression are independent and distinct illnesses. The defining symptoms are nearly identical, and are drawn from the same psychopathologic pool; the conditions overlap substantially, are similar in clinical course, and apparently are indistinguishable in terms of familial aggregation. The diagnostic categories are not stable over time, and the diagnosis often changes if assessed blindly in the future and response to pharmacotherapy and biological findings are not conclusive. Recently Judd et al. (1995) have brought the attention on subsyndromal symptomatic depression based on the presence of two or more simultaneous symptoms of depression present for most or all the time (at least two weeks) in association small dysfunction occurring in individuals who do not meet criteria for diagnoses of minor depression, major depression, and/or dysthymia. Subsyndromal symptomatic depression has a 1-year prevalence in the general population of 8.4%, two thirds of whom are women (63.4%). The most common subsyndromal symptomatic depression symptoms reported are insomnia (44.7%), feeling tired out all the time (42.1%), recurrent thoughts of death (31.0%), trouble concentrating (22.7%), significant weight gain (18.5%), slowed thinking (15.1%), and hypersomnia (15.1%). Increased prevalence of disability and welfare benefits was found in subsyndromal symptomatic depression as compared with respondents with no depressive symptoms.
In a sample of major depressive patients a predictor of recurrence was a co-morbid diagnosis of dysthymia and problems in social functioning. The large Epidemiological Catchment Area (ECA) research in several USA states, has found that the relative risk for first episode of major depression is 4.4 higher in persons with depressive symptoms and 5.5 higher in those with dysthymia than in those without such symptoms or diagnosis (Horwath et al., 1992) suggesting again the same thing, that long lasting depressive mood, including dysthymic disorder is a risk, among other things, for major depression.

Comorbidity and Diagnostic Stability

Comorbidity also raises very important questions. In a sense comorbidity is an artifact of modern nosological approach (modern means post DSM-III). Epidemiological studies show a high overlap of diagnosis in mood disorders. In the Zurich Study (Angst, 1992) the prevalence of pure dysthymia was approximately 1% while together with major depression or recurrent brief depression occurred in 3% of the population. In the DSM-IV mood disorders fied trials (Keller et al., 1995) in a sample of 500 patients who met at least two criteria for major depression, 45% had pure major depression, 22% had major depression and dysthymia and 14% had dysthymia. Furthermore, the diagnostic stability of dysthymia is poor. In the Zurich Study (Angst and Wicki, 1991) of the 19% who had dysthymia in 1986, only 4 had dysthymia 2 years later. The remainder were scattered among subsyndromal depression, major depression and recurrent brief depression. The 4 patients who still had dysthymia had also developed either major depression or recurrent brief depression. This overlapping of major depression and dysthymia led to the concept of double depression: a combination of major depression superimposed on preexisting dysthymia (Keller and Shapiro, 1982; Keller et al., 1983). There is an important co-morbidity with panic disorder, specially when agoraphobia is present (Starcevic et al., 1992) and social phobia, avoidant self-defeating, dependant and borderline personality disorder (Markowitz et al., 1992) and sleep research data suggest that there is a strong biological component in the disorder (Akiskal and Weise, 1992).

The Spectrum of Mood Disorders

The notion that melancholia or bipolar disorders are the common final path of mood disorders in a development which successively includes subsyndromal depression, brief recurrent episodes (depressive or bipolar), cyclothymia, dysthymia and major depression, as proposed by Angst et al. (1992), Akiskal (1991) and Akiskal et al. (1992), belong to this perspective. Epidemiological data suggests that subsyndromal depression and dysthymia are associated to a higher risk for major depression (Horwarth et al., 1992).

In spite of all this difficulties, the concept of dysthymic disorder has been validated by epidemiological and clinical research and may be useful for the clinician who needs to classify in order to take better decisions. The notion of co-morbidity is important for clinical decisions (i.e., the fact of having a dysthymic disorder is a risk for developing major depression, something which will alert the physician not to disregard the importance of a so called “minor depression”).

Coping and Adjustment

Although no studies have been performed, common sense suggests that long lasting depressive moods have to have an impact on the life style of the individual and therefore negative conse-
quences. Indirect evidence from suicide studies suggest that the poor social interaction present in suicide attempters is more common in patients with dysthymia than in other diagnostic groups, and course studies show that functional status is poorer among dysthymics than other depressed groups (Wells et al., 1992). Retirement not due to age and other negative social stresses such as small number of rooms in their home and lack of intimate friendship, moving houses, living in institutions, low social participation, poor family relations and higher presence of detrimental events of an interpersonal nature have been put in relation with the impairment produced by dysthymia. On the other hand, depressive mood has a very important impact on service utilization and social morbidity.

Treatment Outcome
In spite of the diagnostic controversy, “minor” depressives, including dysthymics, respond to drug treatment. Research findings although still preliminary, suggest that MAOIs may be superior to TCAs and that serotonergic antidepressants such as fluoxetine or trazodone are potential agents for the treatment of dysthymia and that dysthymics and major depressives both respond equally to fluvoxamine or maprotiline.

Considering the clinical experience with MAOIs, it is quite understandable that the new reversible MAO-A inhibitors such as moclobemide, have raised expectations in this area, once they have proved efficacy in major depression with or without concomitant dysthymia (Angst, 1992). Again tolerance and safety may be main criteria for treatment choice in a long lasting condition which requires high compliance to prevent relapses.

BASIC DIFFERENCES BETWEEN ICD-10 AND DSM-IV

ICD-10 followed DSM-III and DSM-III-r innovations and the similarities they share are much greater than those present between ICD-10 and its predecessor ICD-9. It is evident that WHO could not ignore such an instrument as DSM-III when developing ICD-10. The number of US scientists and clinicians who have been involved in the development of ICD-10 is extremely high (160 for the Clinical Description and Diagnostic Guidelines version), and vice versa, the number of international experts who have collaborated to DSM, specially to DSM-IV is also very high (almost two hundred).

ICD-10 and DSM-IV were developed according to the same methodology: consensus from expert committees and field trial studies. DSM-IV did also literature reviews and data reanalysis, but although this was not done for ICD-10 the results of worldwide nosological research were taken into account by ICD-10 experts (Sartorius et al., 1993). Furthermore, a special task force was appointed to increase the comparison of DSM-IV and ICD-10 Research version, something which led to important clarifications.

It should be stressed that the differences between ICD-10 and DSM-IV are there because they have to be there. They are unavoidable in the present state of knowledge and some are due to the limitations of classifications based on symptoms. This limitations leave the door open for consensus based decisions where political, public health issues and scientific theories play an important role.
The question of psychiatric diagnosis has to be considered from different perspectives and at present the main criteria should be outcome. Taking into account the difficulties of classification of mood disorders, the approach to the fine specifiers to define clear clinical conditions has an important impact on treatment choice and also on outcome.

Compared to DSM-IV, ICD-10 Clinical Descriptions and Diagnostic Guidelines version is a more flexible system. This may lead to more patients having a positive diagnosis and fewer coming into the residual or atypical disorders categories, something important for health care in general. DSM-IV has stricter criteria, which may lead to higher reliability but also to more patients falling into waste-basket categories. This approach is more relevant for research.

Some particularities of ICD-10 chapter F(V) on Mental and Behavioral Disorders such as the alphanumeric system or the lack of several axes are due to general principles of ICD-10. Of course, there are great advantages of having a psychiatric classification as a part of a general medical one. Due to the limitations of ICD-10 format, chapter F(V) has a separate multiaxial formulation, consisting in three axes: one on Clinical Disorders (including psychiatric disorders, general medical conditions and personality disorders), one on Disablement and one on Environmental Factors. Axis II follows the principle of WHO classification of Impairments, Disabilities and Handicaps (ICIDH, WHO, 1980) and therefore the limitations of function that a disorder produces at the level of the organ, the person or social role are not included among the diagnostic criteria as they depend also on the social conditions, and these change from culture to culture and even in similar settings. In DSM-IV the presence of a disablement is required for most of the psychiatric conditions. The presentations of DSM-IV and ICD-10 are different. DSM-IV consists on the following documents: a single version of the classification, which is multiaxial with a set of criteria for research in the appendix; a shortened edition (pocketbook); a primary health care version and a set of diagnostic instruments. ICD-10, on the other hand consists of several versions: Clinical Descriptions and Diagnostic Guidelines; Diagnostic Criteria for Research; Multiaxial Formulation and Primary Health Care.

PARTICULAR DIFFERENCES REGARDING DYSTHymIA

Dysthymia shares the following characteristics in ICD-10 and DSM-IV: a duration of two years and the presence of common set of symptoms (insomnia, low energy, fatigue, difficulty in concentrating, low self-esteem, loss of interest or pleasure and feelings of hopelessness).

Major Depressive Episode/Depressive Episodes

Both DSM-IV and ICD-10 give clear instructions as to the differentiation of dysthymic and depressive episodes, based on different symptoms patterns, severity and course. In any case, the concurrent presence of criteria for major depression or depressive equivalents excludes the diagnosis of dysthymic disorder.

During the first two years (one year for children and adolescents) of the depressive disturbance, DSM-IV disallows any major depressive episode. If present, individuals are for ever diagnosed as having major depression, eventually subtype as chronic or in partial remission. ICD-10-DRC accepts that “None, or very few, of the individual episodes of depression within such a two-year
The Concept and Classification of Dysthymia

period are severe enough, or last long enough, to meet the criteria for recurrent mild depressive disorder (F33.0).

After two years of dysthymic disorder the presentation of symptoms of major depression will lead to the diagnosis of double depression in DSM-IV while in ICD-10 it may lead to consider the whole disease as a major depression.

The number of symptoms required for diagnosis is different in both systems. DSM-IV requires 2 out of 6, ICD-10-DCR, 3 out of 11 and DSM-IV research criteria, 3 out of 9. If the symptom threshold is set too high it will obscure the boundary with major depression, while if it is too low, it will obscure the boundary with subthreshold conditions, personality disturbances and normal functioning.

The symptoms listed for diagnosis are slightly different. ICD-10-DCR includes “often in tears”, “a perceived inability to cope with the routine activities of every day life” and “less talkative”, while DSM-IV includes “poor appetite or overeating”. DSM-IV-RC adds “irritability or anger”. These differences have a transcultural flavor.

The remission of symptoms is not allowed for more than two months at the same time in DSM-IV, while ICD-10 mentions that “intervening periods of normal mood rarely last for longer than a few weeks”.

The age of onset is considered very differently, because ICD-10-DCR refers to a late onset form “occurring between the ages of 30 and 50 years” whilst DSM-IV-RC sets the cut-off point at “age 21 or older”.

Cyclothymic Disorders

Dysthymic and cyclothymic disorders are clearly differentiated by the presence of hypomanic symptoms, which exclude the diagnosis of dysthymic disorder, although hypomanic switches have been described in dysthymia (Akiskal and Weise, 1992; Markowitz et al., 1992).

Secondary Depression

DSM-IV and ICD-10 include categories for depressive disorders due to psychotropic drugs or medications or to organic or general medical conditions. Here the abuse of the substance or the medical illness have a diagnostic precedence. The same applies for the presence of psychotic symptoms, which are not allowed in any of both diagnostic systems.

Recurrent Depressive Disorder

This disorder is defined by the presence of recurrent brief depressive episodes, occurring about once a month over the past year. Each depressive episode lasts less than two weeks (typically 2-3 days, with complete recovery) but fulfills the symptomatic criteria for mild, moderate or severe depressive episodes. This definition does not allow any confusion with dysthymic disorder, but there are patients who may fulfill criteria for both disorders and therefore they should receive both diagnoses as no set of criteria have been proposed for such cases.

Adjustment and Stress Disorders

The overcoming of the endogenous-neurotic dichotomy allows to better understand the influence of genetic, predisposing and vulnerability factors and of stressful life situations in the origin of mood disorders. But such life events are different from those involved in adjustment and stress...
related disorders. The former are ordinary life circumstances, sometimes very negative but nevertheless ordinary and not everybody will suffer from a clinical condition after experiencing such an event or the association of several ones during a limited period of time. Indeed depressives do not always become depressed again when exposed to other important life changes.

For the diagnosis of stress related disorders, DSM-IV and ICD-10 require that the stressful event or the chronic negative situation are of an extraordinary intensity, such as making any one prone to develop a disorder secondary to it. Stress research has identified several vulnerability factors in such conditions, but the most common ones are of a social nature (López-Ibor Jr., 1985).

ICD-10 uses a time criterium to separate dysthymic disorder and the two depressive categories of adjustment disorders with depressive symptoms.

The duration of brief depressive reaction should not exceed one month and prolonged depressive reaction should not exceed two years. The diagnostic relevance of the adaptation to a significant life change or to the consequences of a stressful life event is less relevant for diagnosis than the time factor. This makes the decisions of the clinicians easier when confronted with depressive patients who are in the vicious circle of a stressful situation which can not be overcome precisely due to the depressive symptoms themselves. In DSM-IV dysthymic disorder takes priority over adjustment disorders.

Nevertheless, this view should coexist with the need to clearly differentiate several categories among the mood disorders, in spite of the often emerging difficulties of this task.

**Other Anxiety Disorders**

The differentiation between anxiety and mood disorders is clearer in western cultures than in other parts of the world where ever the words anxiety or depression may have different meaning or may be absent. This is one of the reasons for the ICD-10 mixed anxiety-depressive disorders category, and for the presence of neurasthenia.

**Mixed Anxiety Depressive Disorders**

ICD-10 has created this mixed category to suit the needs of primary care and of settings where differential diagnosis between anxiety and depression can be difficult. This category should be used when symptoms of both anxiety and depression are present, but either set of symptoms, considered separately, is sufficiently sever to justify a diagnosis. If any set is severe enough to justify a diagnosis of any anxiety or any depressive disorder, the diagnosis should be within one of these categories. If both sets of symptoms are considered separately they would reach diagnostic relevance, both diagnosis should be recorded and if for any reason only one diagnosis can be used, the depression diagnosis is prevalent.

**Neurasthenia**

The category of neurasthenia is not used in many countries and is absent from DSM-IV. ICD-10 recognizes that many of the cases so diagnosed would meet the current criteria for depressive disorder or anxiety disorder, but there are cases that fit into the description of neurasthenia better than that of any other syndrome and such cases seem to be more frequent in some cultures than in others. If the diagnostic category of neurasthenia is used, an attempt should be made first to rule out a depressive illness or an anxiety disorder.
Hallmarks of the neurasthenia syndrome are the patient's emphasis on fatigability and weakness and concern about lowered mental and physical efficiency. Recent literature of Far East countries suggests that these guidelines are already in use, and the clinicians first rule out diagnosis of depression and anxiety disorders before considering the diagnosis of neurasthenia (López-Ibor Jr., 1991).

Panic Disorder
There is an important co-morbidity with panic disorder, especially when agoraphobia is present (Starcevic et al., 1992) and social phobia, avoidant self-defeating, dependant and borderline personality disorder (Markowitz et al., 1992). Nevertheless, and in spite of the traditional thinking, dysthymia is not characterized by the presence of anxiety symptoms, but of long lasting anhedonia. A long range outcome study of panic disorder and generalized anxiety disorder has found several stages of evolution with striking co-morbidity and syndrome change patterns that include depressive episodes, alcoholism and somatization disorders (López-Ibor, Jr. 1988).

Depression in Primary Care
Both DSM-IV and ICD-10 will have a version for primary care use. The WHO classification will consists of a reduced number of categories, which have been chosen because its relevance for primary care but also when known treatments are available for them. In this version all depression categories appear under a single item, F32 depression. This approach may reflect a certain desire of WHO to relief primary care physicians of the burden that we psychiatrists have imposed on ourselves in classifying depressive disorders. Primary care is not a uniform field all over the world, quite the contrary, and most probably ICD-10 and DSM-IV will live together and with other systems such as those developed by primary health care groups.

Personality Disorders and Characterological Problems
The chronic course has raised the question of the role of the personality in dysthymic disorder and of the concept of depressive personality itself. DSM-III dysthymic disorder has absorbed the depressive personality (Peron-Magnan, 1992) although there is still need for a non dysthymic depressive personality disorder category (Klein, 1990). ICD-10 follows the DSM-III approach and the crosswalks between the new version and ICD-9 cleanly state the equivalence of ICD-9 affective personality disorder (301.1) and ICD-10 cyclothymia (F34.0) and dysthymia (F34.1) but leave the door open for other specific personality disorder (F60.8) where depressive or affective personality could be included.

ICD-10 differentiates between Personality Disorders (included in Chapter F, Mental and Behavioral Disorders) and variants of the personality (included in Chapter Z: Factors influencing health status and contact with health services), and this distinction is underlined in the multiaxial version, while DSM-IV still considers a continuity from one to the other. We have put forward many arguments in favor of the usefulness of avoiding this confusion. Personality disorders are still considered under the metaphor of "moral insanity" and the more it is known about a personality disorder the sooner it becomes a disorder of another category, or an axis I disorder in DSM-III (i.e., epileptic personality, depressive personality, schizotypal disorder in ICD-10; López-Ibor Jr., 1993).
Table 1: Kappa coefficients and acceptance of diagnosis by psychiatrists of major psychiatry diagnosis of ICD-10 (summarized for Sartorius et al., 1993)

<table>
<thead>
<tr>
<th>Code and Disorder</th>
<th>K</th>
<th>Nr of patients</th>
<th>Very good or good fit</th>
<th>Very confident or moderately confident</th>
<th>Very easy or moderately easy diagnosis</th>
<th>Good or adequate description</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0 Organic Mental Disorders</td>
<td>.78</td>
<td>224</td>
<td>80.8</td>
<td>89.9</td>
<td>85.3</td>
<td>89.0</td>
</tr>
<tr>
<td>F1 Substance Use Disorders</td>
<td>.80</td>
<td>230</td>
<td>85.2</td>
<td>95.7</td>
<td>88.9</td>
<td>93.4</td>
</tr>
<tr>
<td>F2 Schizophrenic Disorders</td>
<td>.82</td>
<td>733</td>
<td>82.5</td>
<td>91.8</td>
<td>85.9</td>
<td>92.4</td>
</tr>
<tr>
<td>F3 Mood/Affective Disorders</td>
<td>.77</td>
<td>1002</td>
<td>83.7</td>
<td>92.4</td>
<td>86.4</td>
<td>90.9</td>
</tr>
<tr>
<td>F31 Depressive Episode</td>
<td>.66</td>
<td>343</td>
<td>81.8</td>
<td>91.2</td>
<td>84.6</td>
<td>88.4</td>
</tr>
<tr>
<td>F34.1 Dysthymia</td>
<td>.36</td>
<td>101</td>
<td>75.7</td>
<td>86.4</td>
<td>76.3</td>
<td>87.2</td>
</tr>
<tr>
<td>F4 Neurotic Somatoform Dis.</td>
<td>.74</td>
<td>507</td>
<td>79.8</td>
<td>90.2</td>
<td>82.8</td>
<td>88.3</td>
</tr>
<tr>
<td>F5 Physiologic Dysfunctions</td>
<td>.91</td>
<td>67</td>
<td>79.9</td>
<td>87.7</td>
<td>82.8</td>
<td>78.8</td>
</tr>
<tr>
<td>F6 Disorders of Adult Personality</td>
<td>.51</td>
<td>250</td>
<td>68.3</td>
<td>83.1</td>
<td>73.3</td>
<td>80.7</td>
</tr>
<tr>
<td>F7 Mental Retardation</td>
<td>.77</td>
<td>30</td>
<td>96.6</td>
<td>100.0</td>
<td>92.9</td>
<td>93.0</td>
</tr>
<tr>
<td>F9 Disorders of Childhood Onset</td>
<td>.74</td>
<td>79</td>
<td>71.4</td>
<td>80.8</td>
<td>70.1</td>
<td>85.7</td>
</tr>
<tr>
<td>All Diagnostic categories</td>
<td>*</td>
<td>2460</td>
<td>81.5</td>
<td>91.1</td>
<td>84.6</td>
<td>89.9</td>
</tr>
</tbody>
</table>

* : .81 (for 2 characters); .74 (for 3 characters); .59 (for 4 characters)

CONCLUSION

In spite of the difficulties of the historical developments, recent research has provided arguments for the characterization and the differentiation of dysthymia, from the clinical, epidemiological and treatment outcome perspectives. Contrary to the traditional thinking, dysthymia is not characterized by the presence of anxiety symptoms, but by long lasting anhedonia. It begins in early life, has a chronic course, sometimes complicated by major depressive episodes (double depression, Keller et al., 1982). ICD-10 and DSM-IV are both extraordinary productions of modern psychiatric research, even when considered from the global frame of the history of our discipline. The similarities between them are several order of magnitude more striking than differences, but the analysis of these pave the way for fascinating future research.
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CLINICAL EPIDEMIOLOGY OF DYSTHYMIA IN THE WESTERN WORLD

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There is increasing realization that depressive conditions represent a major illness burden in both developed and developing countries (WHO, 1996). There is also increasing evidence that depressive conditions can pursue a chronic course (Akiskal et al., 1981; Keller et al., 1992), thereby compounding the already high personal and social burden of the illness. Dysthymia, now officially sanctioned in both the international classification of diseases (ICD-10, 1992) and the American Psychiatric Association classification of mental disorders (DSM-IV, 1994), is the most prevalent of the chronic depressive conditions.

Based on a five site US (Weissman et al., 1988) and a Swiss study in the canton of Zurich (Angst and Wicki, 1991) it is estimated that 3% of the North American and European population is suffering from this condition. Like major depressive disorder, dysthymia is twice as common in women as men. Characterized by low-grade intermittent chronicity of depression over long period of time, dysthymia is today the prototypical form of the chronic depressive conditions. Although still controversial in some respects (Burton and Akiskal, 1990) consensus is building about the importance of recognizing dysthymia in clinical practice (WPA dysthymia party, 1995).

Dysthymia is distinguished from major depressive disorders by its low grade chronicity over at least a 2 year period. Actually, when first seen clinically, most adult subjects with this condition report depressive symptoms for a decade or longer; indeed, dysthymia often, though not always, begins insidiously in late childhood or adolescence.
The cardinal manifestations of dysthymia include gloomy morosity, anhedonia, low energy, and lack of confidence (Akiskal et al., 1980; Keller et al., 1995); neurovegetative manifestations such as profound weight or sleep disturbances, psychomotor agitation or retardation are typically absent except when a major depressive episode is superimposed on a pre-existing course of dysthymia. The main difference between the ICD-10 and DSM-IV conceptualization of dysthymia is that ICD-10 would permit the concomitance of no more than a few and relatively mild episodes of major depression, whereas in the DSM-IV schema the provision is made for a “double-depressive” pattern whereby dysthymia is complicated by depressive episodes of varying severity and recurrence. Neither manual dwell at length on the complex relationships between dysthymia and such prevalent comorbid conditions as anxiety disorders and medical-neurologic disease. Indeed, the latter might be considered exclusionary criteria in the diagnosis of prototypical dysthyemic disorder. The entire concept of “secondary dysthymia” has actually been dropped from the latest editions of these manuals.

From 1966 to 1980, Index Medicus listed no more than 10 articles on chronic depressions. Since 1980, when dysthymia first appeared in the American Psychiatric Association classification on mental disorders (DSM-III), at this writing (January, 1997) more than 100 articles have appeared on dysthymia alone. This phenomenal growth in research interest parallels the increasing clinical significance of this disorder. This chapter, by invitation, focuses on the emerging clinical epidemiology of dysthymia in the western world.

TOWARD A CLINICAL CLASSIFICATION OF DYSTHYMIA

The foregoing nosological considerations, when applied to the large spectrum of dysthymic subjects observed in different settings, suggest the wisdom of a classificatory schema that is broader than the narrow official concepts of dysthymia, particularly those of DSM-IV. The author and his colleagues (Akiskal et al., 1981), who was among the first to study a very large sample of chronic depressive subjects, made distinctions between different subtypes which, in part, reflected the setting in which these subjects were observed or referred from. Nearly two decades of experience with this group of patients and emerging trends in the literature would suggest a classificatory schema that would subsume the following partially overlapping subtypes:

- Pure “primary dysthymia” - without superimposed or concurrent disorders - is common in untreated community samples, but relatively uncommon in clinical practice (Akiskal et al., 1980). When one does encounter this uncomplicated form of dysthymia in the clinic, it is usually in general medical practice, sleep disorder centers and, to some extent, outpatient private psychotherapy practice. From a public health standpoint, this low-grade uncomplicated form of dysthymia represents an important phase of the disorder, because subjects presenting at this early stage have been found in two prospective studies to be at risk for major depressive episodes (Broadhead et al., 1990. Because dysthymia often makes its first appearance in the juvenile years (Lewinsohn et al., 1992; Kovacs et al., 1994), identifying the disorder at this early stage represents a special opportunity of prevention for child psychiatry and pediatrics.

- The “double-depressive” pattern (Keller et al., 1983), where dysthymia is complicated by recurrent major depressive episodes, is seen primarily in psychiatric settings, including psychiatric
hospitals. This is best viewed as a severe variant of the course of major depressive disorder as emphasized in DSM-IV. Age at onset of dysthymia here, too, is relatively young. At least 80% of clinically ascertained dysthyms have dysthymia. In the community, about 40% meet criteria for major depression (Weissman et al., 1988).

- Dysthymia with various admixtures of anxiety disorders, especially panic disorder and/or social phobic features, is commonly seen in outpatient medical or psychiatric practice (Akiskal, 1983, 1994; Markowitz et al., 1992). Such “comorbidity” may account for 20-30% of dysthyms. This form of dysthymia, which has variable age-at-onset, may uncommonly accentuate to meet the minimum threshold of major depression. This is closest to the ICD-10 concept of dysthymia, and has a bearing on the controversial “anxious-depressive” or “mixed anxiety-depression” constructs. For some European authors (e.g. Tyrer et al., 1992), such co-existing disorders represent a “general neurotic syndrome”.

- In still another group of patients, low grade chronic depressive developments occur in the setting of disabling systemic medical and neurological disorders, and are best categorized as “secondary dysthyms” (Akiskal et al., 1981). The age-at-onset in this type of dysthymia typically parallels that of the medical-neurological condition. For instance, chronic poliomyelitis of childhood onset may not only lead to deformities in musculo-skeletal structures, but could permanently scar the sufferer’s sense of enjoyment, fulfillment, and outlook of life. A more common example of low-grade chronic depressive development secondary to medical-neurologic disease is in the setting of slowly progressive neurodegenerative or non-progressive cerebro-vascular accidents in later life. In both situations, psychological factors might be operative, yet the contribution of specific cerebral lesions to the low-grade subacute or chronic mood state may be substantial. This group as a whole may not meet the strict definition of dysthymia as defined in ICD-10 and DSM-IV, because the low-grade chronic depressive condition occurs in the setting of a well-defined disease, and could be apparent to clinicians over a short period of time, and thus can be diagnosed as a subacute dysthymia-like condition. In these patients, the affective conditions is often disabling, yet severe than major depression; it is low grade, yet not as chronic as dysthymia. Minor depression would not capture the clinical significance of their condition. Many might meet the criteria for subsyndromal depression (Judd et al., 1994). This four-fold classificatory schema, based largely on clinical considerations (Akiskal, 1983), has received recent support in a sophisticated mathematical model known as a numerical taxonomy (Schrader, 1995). The validation of a chronic depressive subgroup secondary either to pre-existing medical-neurologic or nonaffective psychiatric disorders is particularly germane to the theme of this monograph.

ANTECEDENTS OF DYSTHYMIA IN WESTERN MEDICINE AND PSYCHIATRY

Dysthymia, which in classical Greek means “being in bad mood”, is still in current use in that country with the same connotation. In the Hippocratic school, it was considered as part of the broader concept of melancholia (=“black bile”). Indeed, in ancient Greek medicine, what today we call depression was believed to be of biochemical origin. A temperament predisposed to melancholia was also defined (Klibansky et al., 1979); this condition, however, was not called dys-
thymia, and instead labeled "melancholic temperament". It referred to individuals who were lethargic, brooding, and somber (an approximation of what today we consider dysthymic disorder).

It wasn't until the early 19th century that the concept of dysthymia was reintroduced into medicine by the German physicians Stark and Fleming. These authors basically described depressive conditions observed in the hospital that often took chronic course (Brieger and Marneros, 1995). Therefore, the Stark-Fleming dysthymia is quite distinct from the more outpatient presentations of dysthymia that we see today, indeed, in classical European usage, dysthymia often subsumes all mood disorders. The major residue of dysthymia in this classical sense in Europe today is the French usage of the term "les dysthyymes" (Scotto, 1992) as a synonym for all mood disorders or "troubles de l'humeur" ("le trouble dystymique"); by contrast, is reserved for dysthymia in the DSM-IV or ICD-10 definition.

The closest lineage to our current usage of dysthymia in the late 19th century European literature is to be found in the work of Kraepelin (1921), in his concept of the "depressive temperament". This referred either to the relatives of manic-depressives or one of the constitutional antecedents of affective episodes. The condition often began early in life, such that by adolescence many had increased sensitivity to life's sorrows, griefs, and disappointments. They were tormented by guilt, had little confidence in their abilities, and suffered from low energy. As they grew into adulthood, they experienced "life with its activity [as] a burden which they habitually [bore] with dutiful self-denial without being compensated by the pleasure(s) of existence", (p. 120). Although they had excessive need for sleep, they often woke up unrefreshed. Kraepelin stated that in many individuals these temperamental peculiarities were so marked that they could be considered "morbid without the appearance of more severe, delimited attacks..." (clearly foreshadowing the modern concept of more or less pure dysthymia, p. 118). In other cases, he observed that recurrent melancholia arose from this substrate without definite boundaries (again foreshadowing the modern concept of "double-depression"). He further observed that the depressive temperament might serve as "the point of departure for a morbid process... which runs its course in isolated attacks", (p. 118). Kraepelin thus testified to the existence of relatively shorter forms of low grade depressive pathology that pursued their course in intermittent attacks. Although these self-limiting dysthyemic-like attacks were not described to occur in the context of medical-neurological disease, their very description suggests that low grade subacute depressions could present as a morbid affective process without necessarily being chronic.

Kraepelin's concepts of the depressive temperament had further development in Kurt Schneider's delineation of the "depressive psychopath" (1958): the entire existence of these individuals is submerged in suffering - indeed, they believe they belong to an "aristocracy of suffering". Although Schneider, like Kahn (1931), Kretschmer (1936), and Tellenbach (1980) devoted extensive descriptions to individuals with depressive and melancholic traits, he did not provide diagnostic criteria. The work of classical psychopathologists represents a rich phenomenologic tradition that the author and his Memphis associates have used as a framework for understanding and describing the dysthyemic group of patients which are seen in contemporary practice.

Our work, conducted at the University of Tennessee in the 1970s, led to the operationalization of the construct of a depressive or dysthyemic temperament, consisting of the traits listed in Table 1. These traits basically identify gloomy individuals given to brooding and pessimism, who are preoc-


Clinical Epidemiology of Dysthymia in the Western World

Table 1: The depressive or dysthymic temperament

- Gloomy, somber and incapable of having fun
- Brooding, self-critical and guilt-prone
- Lack of confidence, low self-esteem, preoccupation with failure
- Pessimistic, easily discouraged
- Easy to tire, sluggish and bound to routine
- Nonassertive, self-denying and devoted
- Shy and sensitive

University of Tennessee Operationalization (updated from Akiskal, 1983)

ocupied with failure. Similar concepts have also appeared in the Japanese literature (summarized in Kasahara, 1992), with particular emphasis on self-critical attitudes and devotion to others. Finally, the construct of “la depression constitutionelle”, developed in France (Montassut, 1938; Peron-Magnan, 1991), has emphasized the lethargic aspects with a sense of inadequacy.

To sum up these historic developments in light of what today we consider dysthymia, for nearly 2,500 years physicians and psychiatrists have described individuals with a low grade chronic depressive profile marked by lethargy, gloominess, pessimism, low enjoyment of life, relatively low drive, yet endowed with self-critical attitudes and devotion to others. These traits have been defined as constitutional or temperamental characteristics related to melancholic diseases, though not in an obligatory fashion. That is, clinicians have recognized that such individuals exist without necessary progression to clinical or hospitalized depression. This is compatible with a spectrum concept of depressive illness, which defines various degrees of severity and handicap (Akiskal, 1983). Historically, physicians and psychiatrists in the western tradition have described these patients in the different settings in which they observed them. To the contemporary observer, it may seem confusing that the term “dysthymia” has been used for both severe inpatient depressives, as well as the untreated relatives of the affectively ill. Yet, in our contemporary usage of the term “dysthymia” in the U.S. and the international classification system, the entire spectrum of severity is implied - from dysthymia to double depression. In a sense, psychiatrists have always debated whether dysthymia and melancholia refer to similar or distinct patients (Kendell, 1976). Clinical reality has shown that they may occur independently or co-occur together. There is increasing realization today that dysthymia behaves in a trait-like fashion (Akiskal, 1996), predisposing to major affective episodes (including those with melancholic severity), or may continue throughout life without transformation into another condition.

However, the classical authors did not make specific reference to dysthymia occurring in the context of medical-neurologic disease. The latter were usually assigned to the now defunct category of “involutional melancholia” that pursued a severe chronic course. It is of interest to us today that Kraepelin hypothesized this condition - that filled psychiatric hospitals in the first half of this century - to result from age-related vascular and cerebral factors. Again, the parallel to the contemporaneous “secondary dysthymias” is tenuous: yet, it is striking that the advent of brain
imaging coupled with the precise measurement of depression has led to the identification of dysthymic-like low grade depressive conditions in the setting of disabling neurologic and cerebrovascular conditions.

CONTEMPORANEOUS VALIDATION OF DYSTHYMIA AS A FORM OF AFFECTIVE PATHOLOGY

The concept of melancholic or depressive temperament, the forerunner of today's concept of dysthymia, as it developed in continental Europe referred to a form of affective pathology with a constitutional tendency to melancholia. It is an affective construct with biological underpinnings (Akiskal, 1994). This conceptualization, while dominant in the early part of the century, gradually disappeared from psychiatric thinking throughout the remainder of the 20th century. One reason was that Kurt Schneider (1958) preferred to conceptualize this form of pathology as "psychopathy", by which he meant abnormal personality development. Freud's disciples, independently, took this one step further and, eventually, all milder outpatient depressions with tendency to chronicity came to be considered as the expressions of a "character neurosis" (Arieti and Bemporad, 1980).

In support for this position, psychodynamically inclined authors could point to the long-standing nature of the emotional difficulties in individuals with such pathology, the interpersonal problems so common in their lives, and the impression that somatotherapy gave more side effects than benefits to such patients. When and if antidepressants were used, they were given in homeopathic doses; worse, many patients received stimulants or benzodiazepines rather than genuine antidepressants (Weissman and Klerman, 1977). Failure to respond to these incorrectly chosen pharmacological agents further seemed to reinforce the notion of a "character disorder" as the underlying pathology in these long-term, low grade sufferers of depression (Akiskal et al., 1978). Indeed, many of these patients considered themselves as "having been depressed all of their lives"; their gloom generalized to everything from their work to their spouses and children, and therapists (Akiskal, 1983). They were satisfied with nothing and spoke of the "uselessness of existence" and, when occasionally given pharmacologic treatments, they overdosed on them. For all these reasons, psychodynamic psychotherapy that went to the "root" of their problems was preferred over "symptomatic" treatments (so went the argument).

Several lines of observation led the author to challenge the concept of "character neurosis" as an explanation for low grade depression, and thereby forced a return to the more classical European concept of temperament. As a young physician, the author observed low grade depressive conditions that pursued a course of fluctuating chronicity such that depression could not be distinguished from their habitual selves. In the official American nomenclature of the day (DSM-II), they were referred to as chronic "depressive neuroses" and more colloquially, as "characterologic depressions" (Akiskal et al., 1980). As a young psychiatrist in charge of the University of Tennessee Mood Clinic, the author and his colleagues (Akiskal et al., 1978) conducted a 3-4 year follow-up study of 100 neurotic depressives, and found that as many as 22% developed melancholic and/or severe psychotic depressions, and another 18% became bipolar. Such data favored the idea of a continuum between the milder and more severe depressive disorders; more importantly, our results suggested
that low-grade chronicity of depression could serve as a substrate of major depression. This finding has been replicated in a German study (Bronisch et al., 1985).

At the University of Tennessee affiliated Baptist Hospital Sleep Disorder Center, we also had the occasion to examine in great detail REM sleep parameters, especially REM latency (the time from onset of sleep to that of first REM period), in a young man referred to rule out narcolepsy or sleep apnea. He had neither, but had abnormally shortened REM latency. Given that he was in psychotherapy for a "depressive character neurosis", we considered the possibility that the laboratory findings of short REM latency indicated a biological diathesis for depression. This was tested in 12 other subjects with similar "characterologic" problems (Akiskal et al., 1980). These subjects were not suffering from clinical major depression, yet their sleep was, in 5 cases, similar to the first patient. In a subsequent study, we observed 20 patients with tendency to hypersomnia and relative preservation of delta sleep and circadian redistribution of REM sleep to the early part of the night with resultant shortened REM latency. These findings were present in primary dysthyms with and without past history of major depression, but not in dysthyms with antecedent anxiety disorders. Family history for major affective illness (including bipolar) was significantly high in short REM latency dysthyms (Rosenthal et al., 1981). The findings of sleep pathology were so reminiscent of those seen in major affective illness (Kupfer, 1976), that we were compelled to give the dysthymic subjects systematic open trials with desipramine and norriptpyline (the best tolerated secondary amine tricyclics in those days) or lithium carbonate if both antidepressants given in sequence failed (this was based on our observation of bipolar disorder in their families as noted above). We reported good response to these pharmacological approaches (when coupled with practical psychotherapy) in 40% of the dysthymic subjects; one out of three of pharmacotherapy-responsive dysthyms developed brief hypomania. These results were impressive, especially in light of the fact that most of them had failed to respond to years of long-term psychotherapy. We hypothesized that these patients' depressive inertia, anhedonia, and gloom at a temperamental level had prevented them to benefit from psychotherapy; reversal of these disturbances with pharmacotherapy, made them responsive to brief psychotherapeutic approaches focusing on their interpersonal and vocational goals.

The foregoing studies led us to the conclusion that "character neurosis" with intermittent depressive symptomatology represents a true subaffective disorder. We felt that "dysthymia" was an appropriate term for this condition because it had the classical connotation of a dysregulated affective process, manifesting in this instance at a low-grade level. Frank personality disorders, which occur in 40-50%, often appear secondary to this low-grade intermittent affective process.

That dysthymia arises in childhood has been shown definitively by Kovacs and colleagues (1994) who examined 6-9 year old low grade depressives, and followed them for up to 12 years. Strikingly, in many, dysthymia had an episodic course, albeit with short intervals of normalcy (as Kraepelin had described). Over time, superimposed major affective episodes (including bipolar transformation) occurred in 75%. The tendency to bipolarity in a subgroup of dysthyms is a clear indication of the link of dysthymia to affective disorders. Bipolar switching has also been shown in young adult dysthyms in places as far apart as New York (Klein et al., 1988b) and Nagoya, Japan (Furukawa et al., 1993). Finally, Rihmer (1990) has shown that Hungarian dysthyms treated with sleep deprivation often developed brief hypomanic switching.

The familial predisposition to dysthymia has been documented by the high rates of dysthymia in
the offspring of the affectively ill (Akiskal et al., 1985; Klein et al., 1988a). Most importantly, Klein et al. (1995) have shown high rates of affective illness in a systematic familial investigation of dysthymic probands. The familial link to bipolarity has been replicated by Cassano and Savino (1993).

In a review of biological investigations dysthymia, Howland and Thase (1991) concluded that REM latency, TRH-TSH challenge, and electrodermal activity comparable to those with major depressive disorders, were the main findings; by contrast, DST and catecholamine metabolism were essentially unaltered in dysthymia. These data, from a biological standpoint, suggest that dysthymia represents a trait depression. Coupled with the previously reviewed family history data, this traitiness can be viewed to be of constitutional origin. Certainly, the occurrence of major affective episodes in the long-term course of dysthymia, in both community and clinical samples, is in line with this position. It is of great theoretical and practical significance, in light of these considerations, that shortened REM latency has been reported in the offspring of adults with affective disorder (Giles et al., 1988).

The trait nature of dysthymia can be further observed in the fact that dysthymia often pursues an unrelenting course towards chronicity. Thus, spontaneous recovery has been shown to occur in no more than 18% over one year, and that pertains to subjects in the community. In outpatient clinics, the outcome is somewhat better, with 46% recovery, but this is probably due to treatment received and longer follow-up. It is felicitous that new developments in psychopharmacology are being increasingly applied towards the alleviation of the suffering of dysthymic patients, and have been shown to be effective for both the dysthymia and the superimposed depression (Kocsis et al., 1988; Stewart et al., 1989; Ravindran et al., 1994; Stabl et al., 1989; Boyer and Lerubier, 1996).

Much of what has been summarized from the literature on dysthymia in this chapter pertains to so-called “primary dysthymia”. As discussed in the early part of this chapter, dysthymia often occurs in the context of anxiety disorders, as well as alcohol and substance abuse. In collaboration with clinical investigators at the University of Pisa (Perugi et al., 1994), we have recently reported that “primary dysthymia” is more disabling - as far as quality of life in social and personal areas, work, and leisure - than chronic depression occurring in the setting of a severe anxiety disorder like agoraphobia. Celibacy too, is common in early onset dysthymia (Akiskal, 1983). The present author is not aware of comparisons of dysthymia with and without alcohol and substance abuse.

**DYSTHYMIA AND MEDICAL-NEUROLOGIC DISEASE**

More germane to the central theme of this WHO monograph are the studies of depressive symptoms in general medical practice. Actually, the most important of these studies (Wells et al., 1989) focused on depressive symptoms falling short of the major depressive threshold as far as symptom intensity, as well as falling short of the 2 year duration criterion for dysthymia. Such patients often complain of fatigue, poor memory, or unrefreshed sleep. Despite the low grade nature of their depressive complaints, these patients had high degrees of morbidity and impairment in a variety of health domains and quality of life, including “bed days”, i.e. number of days per year they stayed ill in bed. Actually, these impairments were generally more pronounced than those of patients with a
variety of medical conditions, such as hypertension, diabetes, arthritis, and chronic lung disease; only coronary artery disease exceeded the disability of low-grade depression in several domains.

This brings us to the topic of dysthymia secondary to medical-neurologic disease. This topic has only received scant attention in the literature. This monograph is the first international conference focusing on this topic. As suggested earlier, conceptually, one may think of childhood onset, systemic and/or neurologic disease that may lead to dysthymic-like developments in the sufferer; or disabling systemic or neurologic diseases occurring in late life and directly impacting on the brain with secondary low-grade depressive manifestations. Indeed, a recent paper on late life dysthymia (Devenand et al., 1994) has reported high prevalence of medical disease. Biological investigations of medical-neurologic depressions, especially those with dysthymic features are scant. This is due to the heterogeneity of the contributing medical-neurologic diseases, as well as the fact that the presence of such disease is usually an exclusion for the diagnosis of dysthymia (e.g., DSM-IV, 1994). Indeed, their pathophysiology appears distinct from that of primary dysthyrias. A study conducted in our laboratory (King et al., 1981), for instance, has shown REM sleep (the actual density of eye movements during REM sleep) to be significantly decreased in medical-neurologic depressions; this contrasts to increased REM density in primary depressive disease. (In many cases, there seems to be an inverse relationship between REM density and REM latency).

In our 1981 paper reporting on a study of 137 chronic depressives, we identified 38 (28%) with medical-neurologic disease (Table 2). Although neurologic conditions were the most common, stroke was relatively uncommon. This subject has subsequently received extensive research attention (Starkstein and Robinson, 1993). The paucity of stroke in our sample is probably due to the fact that prior to the pioneering work of these investigators, there was no reliable way to measure depressive symptoms in post-stroke patients. Another noteworthy association of clinical significance in our 1981 study is that joint medical-neurologic and non-affective psychiatric disease contributed to extreme refractoriness to the chronic depressive state of these patients. Two of these actually committed sui-

---

**Table 2: Chronic depression and medical-neurologic diseases**

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Neurologic Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy (4)</td>
<td>Amputated leg, bone neoplasm (1)</td>
</tr>
<tr>
<td>Stroke (2)</td>
<td>Congestive heart failure (5)</td>
</tr>
<tr>
<td>Operated atriovenous fistula (1)</td>
<td>Multiple birth defects (2)</td>
</tr>
<tr>
<td>Huntington's chorea (1)</td>
<td>Systemic lupus erythematosus (1)</td>
</tr>
<tr>
<td>Operated brain neoplasm (1)</td>
<td>Chronic obstructive lung disease (2)</td>
</tr>
<tr>
<td>Spinocerebellar degeneration (1)</td>
<td>Renal tubular acidosis (1)</td>
</tr>
<tr>
<td>Multiple sclerosis (1)</td>
<td>Peptic ulcer (1)</td>
</tr>
<tr>
<td>Postencephalic dystonia (1)</td>
<td>Aplastic anemia (1)</td>
</tr>
<tr>
<td>Chronic poliomyelitis (1)</td>
<td>Abnormal cancer (2)</td>
</tr>
<tr>
<td>Degenerative arthritis of spine (1)</td>
<td>Thyroid disease (2)</td>
</tr>
<tr>
<td>Rheumatoid arthritis (5)</td>
<td>Glaucoma with total blindness (1)</td>
</tr>
</tbody>
</table>

Summarized from Akiskal et al. (1981)
cide: both were women with severe somatization disorder, one complicated by epilepsy and alcoholism, and the other by degenerative arthritis of the spine and heavy sedative hypnotic dependence.

In the subsample with medical-neurologic disease, full recovery from preexisting depression was prevented in nearly half by such disease; these were most commonly of a hypertensive, orthopedic or rheumatologic nature. Interestingly, living with a medically disabled spouse or family member, too, delayed recovery from depression in 8 (6%).

Scott et al. (1988) have shown hypothyroidism to be common in chronic depressives. In our experience this typically consists of borderline hypothyroidism, and is most prevalent in early onset dysthymic patients attending mood clinics. That is, thyroid disturbances seem to characterize dysthyrmias presenting with refractoriness to a specialized mood disorder center.

CONCLUDING REMARKS

Epidemiologic studies in the US and Europe have demonstrated that the point prevalence of dysthymic disorder is at least 3% of the general population. Under different names, dysthymia has for 2,500 years described individuals with low grade depressive symptoms including gloominess, anhedonia, anergia and reduced drive, low self esteem and pessimism. Because of its chronic fluctuating nature, dysthymia is among the most prevalent conditions encountered in general medical and psychiatric practice. Although untreated dysthymia in the community often exists in “pure” form, patients consulting their physicians typically present in a more complex fashion. These complex presentations include comorbidity with such disorders as panic, social phobic, alcohol use, and eating disorders (20-35%). Another very common clinical presentation of dysthymia is double depression (50-80%), that is when the low-grade dysthymia has been complicated by major depressive episodes. In view of the chronic - often lifelong - nature of dysthymia and the associated comorbidity, avoidant and dependent personality developments are commonly reported in dysthymia (40-50%). It is noteworthy that in both epidemiological and clinical populations, dysthymia has been found to be chronologically the “primary” disorder. Indeed dysthymia often begins insidiously in childhood and adolescence.

Another pattern of dysthymia - or low-grade subacute and chronic depression - is a late onset variety occurring in the setting of disabling medical and neurologic disorders, and/or associated with retirement and social handicaps. The common theme of these medical-neurologic disorders are deficits in locomotion, e.g. rheumatologic, orthopedic, slowly progressive cerebral disease or arrested neurologic disease (such as history of poliomyelitis, encephalitis, stroke). Other disorders include epilepsy, sleep apnea, and cardiovascular disease. Hypothyroidism can also underlie chronicity of depression presenting to specialized mood clinics.

In the psychiatric literature, the foregoing “secondary” cases with medical-neurologic disease are usually exclusion criteria for the diagnosis of dysthymia. As a result, most of the studies based on the American Psychiatric Association and World Health Organization diagnostic criteria (e.g. DSM-III, DSM-IV and ICD-10) have focused in primary dysthymia. Serious handicaps - e.g. in leisure functions, social roles, absenteeism from work, and frequent medical consultations for unexplained physical symptoms - have been described in these patients generally exceeding that observed in patients with such medical disorders as hypertension, diabetes, and cardiopulmonary disease.
Dysthymics typically work hard, but they do not enjoy their work. Celibacy is common, because of deficits in social skills; if married they are deadlocked in bitter and unhappy marriages which lead neither to reconciliation nor to separation. For them, their entire existence is a burden; they are satisfied with nothing, complain of everything, and brood about the uselessness of existence. As a result, physicians - including psychiatrists - often find it difficult to deal with these patients who might be labeled “existential depressives” or “depressive characters”. Nonetheless, traits biologic findings - especially disturbances in circadian REM sleep parameters - have been reported in primary dysthymia. Furthermore, family studies of dysthymia have demonstrated a significant excess of major affective disorders. Such studies - and the fact that dysthymia is often complicated by major affective episodes - do suggest that dysthymia is best conceptualized as a “trait” depression, as a constitutional depressive diathesis that predisposes to more severe depression. These considerations in turn have provided the rationale for controlled antidepressant trials in dysthymia. These trials have shown response rates comparable to those in major affective disorders. In addition, sleep deprivation has been reported to lead to transient uplifting of the gloomy-lethargic disposition of these patients. Finally, responses to various treatments sometimes entitl brief hypomania.

While dysthymia is in some ways qualitatively distinct from major affective disorders (being dominated by cognitive-emotional disturbances), it shares many clinically relevant and trait biologic dysfunctions that make it a legitimated mood disorder. It is certainly not a “minor” condition, and its pervasive pathology and handicaps place it at the forefront of public health. More studies should be conducted to validate clinical subtypes, because it is likely to be heterogeneous. This is particularly likely to be the case for the secondary and subacute dysthymic-like conditions observed in the context of neurologic disease. The naturalistic outcome (of untreated) dysthymia is grave. Clinical considerations do suggest that it might also considerably aggravate the prognosis of co-existing medical and neurologic disorders. For all these reasons dysthymia, whether primary or secondary, deserves laboratory, clinical and public health attention.

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26
DYSTHYMIA IN CHILDREN

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INTRODUCTION

In children, dysthymia often results in decreased school performance and impaired social interaction. Children with dysthymia are usually irritable and cranky and may have feelings of depression with low self-esteem, poor social skills and pessimism.

This presentation includes:
1. Epidemiology of dysthymia in children
2. Biological basis of dysthymia in children
3. Clinical features of dysthymia in children
4. Treatment and prognosis of dysthymia in children

PREVALENCE OF DYSTHYMIA IN CHILDREN

The diagnosis of dysthymia in children was higher in private psychiatric hospitals during the Persian Gulf crisis (Levai et al., 1994). Sexually abused girls had a greater incidence of dysthymia than control girls (De-Bellis et al., 1994a, 1994b). The lifetime and current prevalence of dysthymia were significantly greater in the children with ulcerative colitis than those with Crohn's disease (p<0.01) or cystic fibrosis (p<0.01) (Burke et al., 1989). Dysthymia was a subtype of depression in children after recovery from severe burns (Stoddard et al., 1992).

RISK FACTORS OF DYSTHYMIA IN CHILDREN

Family environment plays an important role in the occurrence of dysthymia (Warner et al., 1995). Not living with both natural parents (OR = 14.67) and socioeconomic status (OR = 0.44) were significant correlates of dysthymia (Garrison et al., 1992). A history of early separation experiences is less likely a risk factor for dysthymia than for borderline personality disorder (Zanarini et al., 1989).
Table 1: Prevalence of dysthymia in children

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence</th>
<th>Sample size</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canals-J, 1995, Spain</td>
<td>1.4% in girls</td>
<td>507</td>
<td>11-12 years</td>
</tr>
<tr>
<td></td>
<td>0.8% in boys</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polaino-Lorente-A, 1993, Spain</td>
<td>6.4%</td>
<td>6432</td>
<td>8-11 years</td>
</tr>
<tr>
<td>Garrison-CZ, 1992, United Stades</td>
<td>7.9% in girls</td>
<td>3283 adolescents,</td>
<td>12-14 years</td>
</tr>
<tr>
<td></td>
<td>5.0% in boys</td>
<td>488 mother-child pairs</td>
<td></td>
</tr>
<tr>
<td>Kaufman-J, 1991, United Stades</td>
<td>25%</td>
<td>56 maltreated children</td>
<td>7-12 years</td>
</tr>
</tbody>
</table>

BIOLOGICAL BASIS OF DYSTHYMIA IN CHILDREN

Children with dysthymic disorder had a lower rate of nonsuppression (29%) than children with major depression (69%) in the dexamethasone suppression test (DST) (Stein et al., 1994). Urinary catecholamine excretion and hypothalamic-pituitary-adrenal axis dysregulation may be related to dysthymia (De-Bellis et al., 1994a, 1994b). Additionally, high plasma dopamine-beta-hydroxylase (D beta H) has been related to dysthymia (Rogeness et al., 1988).

There were no correlations between neuroendocrine parameters of dysthyrmics and degree of depression, age, sex or weight, age of onset, duration and family history of dysthymia (Brambilla et al., 1989).

CLINICAL CHARACTERISTICS

Compared to the major depression and double depression groups, more often externalizing disorders and more impaired social functioning were present in the dysthymic group. Chronicity of dysthymia seems to be the determining factor in social functioning (Ferro et al., 1994).

Childhood-onset dysthymic disorder may be an early marker of the recurrent affective illness. Dysthymic children who have subsequent mood disorders are most likely first to have an episode of MDD, and that episode appears to be the "gateway" to the recurrent affective illness. The interval between the onset of dysthymia and the first major depression may provide a window of opportunity for intervention and possible prevention of later episodes (Kovacs et al., 1994).

A previous comorbid diagnosis of dysthymia was one of the predictors of the recurrence of major
Dysthymia in Children

Table 2: Dysthymic symptoms in Chinese children

<table>
<thead>
<tr>
<th>2432 children aged 7-13 years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritable</td>
<td>1.85%</td>
</tr>
<tr>
<td>Poor appetite or overeating</td>
<td>2.47%</td>
</tr>
<tr>
<td>Insomnia or hypersomnia</td>
<td>0.12%</td>
</tr>
<tr>
<td>Low self-esteem</td>
<td>0.90%</td>
</tr>
<tr>
<td>Poor concentration</td>
<td>3.99%</td>
</tr>
<tr>
<td>Difficulty making decisions</td>
<td>1.56%</td>
</tr>
<tr>
<td>Feelings of hopelessness</td>
<td>0.33%</td>
</tr>
</tbody>
</table>

| 2067 children aged 3-7 years   |  |
| Depressed mood                 | 1.8% |
| Low energy or fatigue          | 2.9% |

depression (Warner et al., 1992b). There was a high rate of comorbidity in children and adolescents between depression and dysthymia (Angold and Costello, 1993). Psychiatric comorbidity in children with dysthymia includes trichotillomania and conduct disorders (Reeve et al., 1992; Kovacs et al., 1988). The more severely anxious children had higher rates of dysthymia (Kashani et al., 1990). Dysthymic disorders were associated with significantly higher rates of suicidal behaviors than were adjustment disorder with depressed mood nondepressive disorders (Kovacs et al., 1993).

TREATMENT AND PROGNOSIS

Statistically significant improvements were observed for the combination of several antidepressants (Desipramine and Methylphenidate), in comparison to placebo, beyond those seen with either drug alone. However, the clinical improvements were modest. There was no evidence that stimulant medication and DMI potentiated each other’s effects in treating symptoms of major depressive disorder or dysthymic disorder. Compared to placebo, there was no differential efficacy of DMI and MPH for treating symptoms of dysthymic disorder (Carlson et al., 1995). The short-term outcome in dysthymia was good (80.6%). Probability of recurrence was 35.7% (Bouvard et al., 1993). The functioning of children with dysthymic disorder was improved over time compared to that with aggressive or antisocial behaviors (Verhulst et al., 1993).

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EPIDEMIOLOGY OF DYSTHYMIA IN SOUTH AMERICA

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There is very limited information about the epidemiology of mental disorders in South America. The continent is heterogeneous in many demographic, socio-economic and cultural aspects, and the available data may have low external validity. No probabilistic sampling was ever carried out to my knowledge, and even the probability of intra-national variability remains undetermined.

I shall present data from two Brazilian epidemiological studies with information on the prevalence of dysthymia. The first was carried out by Almeida-Filho et al. (1992), in 6470 adults of 3 large cities in different regions of the country: Brasília (Nr=2344), São Paulo (Nr=1742) and Porto Alegre (Nr=2384), using a 45-item screening questionnaire (Q.M.P.A.) followed by an inventory for DSM-III symptoms. The one-year prevalences for DSM-III mental disorders in general and for dysthymia are given in Table 1.
Table 1: One-year prevalence (%) of DSM-III disorders in 3 Brazilian cities (Nr=6470; Q.M.P.A.; Almeida-Filho et al., 1992; Andreoli, pers. commun., May 1996).

<table>
<thead>
<tr>
<th></th>
<th>ANY DISORDER</th>
<th>DYSTHYMIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRASÍLIA</td>
<td>male 47</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>female 27</td>
<td>2.7</td>
</tr>
<tr>
<td>SÃO PAULO</td>
<td>male 33</td>
<td>----------</td>
</tr>
<tr>
<td></td>
<td>female 29</td>
<td>3.2</td>
</tr>
<tr>
<td>PORTO ALEGRE</td>
<td>male 35</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>female 50</td>
<td>6.5</td>
</tr>
</tbody>
</table>

The second (Andrade, De Lolio, Gentil, Laurenti & Werebe, in preparation), is an ongoing study of the lifetime prevalences of ICD-10 mental disorders in the catchment area of our Institute in the city of São Paulo, a 12 million inhabitants metropolis in the south-east of the country.

According to a 1991 census, our catchment area had 91,710 middle class inhabitants, living in 28,169 flats and houses, in two districts with a total area of 10.5 square kilometers. The adult population (77.1% aged 18 years and above) consisted of 70,743 people (45.4% males), resulting in an estimated rate of 2.5 adults per household.

The sample size was determined using the E.C.A. lifetime prevalence for mania (0.8%) and a 5% significance level, and was increased in 33% for missing values, resulting in 1,626 households. An oversample for old and young people was carried out by interviewing all residents of or above 60 years of age and those aged 18 to 24 years.

Psychopathology was assessed by the Composite International Diagnostic Interview (CIDI), conducted by trained lay interviewers, and the ICD-10 prevalence rates were adjusted for the effects of the oversampling. In a second stage, currently in progress, these individuals and a subsample of negative CIDI subjects are being submitted to a psychiatric interview (SCAN).

Table 2 presents overall results from the first 1189 interviews (42.4% males) carried out so far. Table 3 presents the adjusted lifetime prevalences of depression and dysthymia by sex and age.

The decrease in the prevalences of depression above the age of 45, observed for both sexes and consistent with other studies (Wittchen et al., 1994), was not detected for dysthymia in women, and the peak in males aged 45-59 is being re-assessed.

Therefore, both Brazilian studies resulted in estimates for dysthymia within the range found in the literature, but the validity of these results for other South-american countries and for the general population of Brazil requires confirmation, as they were conducted in metropolitan areas of large developed cities, with ethnic, cultural and socio-economic differences with other countries and regions of the sub-continent.

Different from the more developed countries, primary care for mental disorders is still poorly organized, even in large cities, and a repressed demand for treatment is readily apparent.

For instance, in a recent study in our Institute (Gorenstein et al., submitted), we advertized...
Table 2: Adjusted lifetime prevalences for ICD-10 mental disorders in a catchment area in São Paulo (N=1189; CIDI; Andrade et al., in preparation)

<table>
<thead>
<tr>
<th>ICD-10 DIAGNOSIS</th>
<th>PREVALENCE %</th>
<th>ICD-10 DIAGNOSIS</th>
<th>PREVALENCE %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Disorder: males</td>
<td>40.5</td>
<td>F34.1 Dysthymia</td>
<td>4.1</td>
</tr>
<tr>
<td>females</td>
<td>43.0</td>
<td>F44 Dissociative</td>
<td>2.6</td>
</tr>
<tr>
<td>F17.2 Nicotine</td>
<td>24.5</td>
<td>F20 Schizophrenia</td>
<td>1.6</td>
</tr>
<tr>
<td>F32-33 Depression</td>
<td>14.8</td>
<td>F11-19 Other drugs</td>
<td>1.1</td>
</tr>
<tr>
<td>F40 Phobic Anxiety</td>
<td>8.8</td>
<td>F50.9 Bulimia</td>
<td>1.1</td>
</tr>
<tr>
<td>F10 Alcohol</td>
<td>5.6</td>
<td>F30-31 Bipolar</td>
<td>0.8</td>
</tr>
<tr>
<td>F41 Other Anxiety</td>
<td>4.9</td>
<td>F42 Obsessive-compulsive</td>
<td>0.2</td>
</tr>
<tr>
<td>F45 Somatoform</td>
<td>4.6</td>
<td>F25.1 Schizoaffective</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Table 3: Lifetime prevalences for depression and dysthymia (N=1189; CIDI; Andrade et al., in preparation).

<table>
<thead>
<tr>
<th>SEX AND AGE GROUP</th>
<th>DEPRESSION F32-F33</th>
<th>DYSTHYMIA F34.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>15.2</td>
<td>2.9</td>
</tr>
<tr>
<td>18-24</td>
<td>3.9</td>
<td>1.3</td>
</tr>
<tr>
<td>25-44</td>
<td>17.3</td>
<td>0.9</td>
</tr>
<tr>
<td>45-59</td>
<td>13.7</td>
<td>10.1</td>
</tr>
<tr>
<td>60 &amp; over</td>
<td>4.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>16.8</td>
<td>5.1</td>
</tr>
<tr>
<td>18-24</td>
<td>8.1</td>
<td>0.6</td>
</tr>
<tr>
<td>25-44</td>
<td>22.3</td>
<td>5.0</td>
</tr>
<tr>
<td>45-59</td>
<td>18.1</td>
<td>7.5</td>
</tr>
<tr>
<td>60 &amp; over</td>
<td>9.3</td>
<td>6.2</td>
</tr>
</tbody>
</table>

requests for “Normal volunteers with high school or further education, with mild anxiety or irritability but no significant social or work impairment, for a clinical trial of an antidepressant in normals”. Out of 254 applicants submitted to the Self-Report Questionnaire (SRQ-20), only 93 (36.6%) scored below the cut-off level for psychopathology. Of these, 58 were further evaluated by a clinical psychiatric interview and a PSE-10/SCAN, and 38 (65.5%) met ICD-10 criteria for one or more psychiatric diagnoses. Major depression (55%), dysthymia (16%), phobias (13%), panic (5%), and
cyclothymia (5%) were the most common disorders. Worth noting, 35 (90.5%) of these individuals had never sought or received any psychiatric evaluation or care.

Public education and training programs are urgently needed, and some are in progress in various South-American countries. Concerns have been raised about attempts to simply translate and apply the experience gathered in other regions of the world to South America, and I would like to mention a few differences from our practice of psychiatry in relation to some apparent tendencies in the international programmes on depression and dysthymia currently available in our region.

The first is related to the fact that we speak Spanish or Portuguese, and that we received a strong influence from France, Spain and Portugal. Of relevance for the diagnosis of depression and dysthymia, both in South America and in Latin Europe, much importance is attributed to the psychopathological concept of “Angústia”.

“Angústia” has no counterpart in Anglo-American psychopathology, and is encompassed by the word “Anxiety”. Aubrey Lewis (1979) remarked that the French term “angoisse” “...was more critically examined and more discriminatively used than the German term Angst, on which British and American psychiatrists have relied, accepting its deceptively close translation as anxiety” (p.78).

Lewis mentions the contribution of E. Pichon, a follower of Pierre Janet: “For him angoisse is a process in which intense and acute mental suffering synchronises with a subjective sense of constriction of the throat, tachycardia, and other visceral disturbances...” (p.78). He also quotes López-Ibor, who wrote the most comprehensive book on “Angústia” available to date: “...the fact that there is only one word Angst has relieved the Germans of any necessity to separate and distinguish between angustia and ansiedade... The great influence of the German psychiatrists has led many other authors to forget such distinctions, even outside the German tongue... In Spanish angustia and ansiedad are now used indifferently, because of the influence of foreign languages” (Lewis, 1979, p.76).

Most well trained psychiatrists in Latin-America have learned the value of the concept of “Vital Angústia”, which for López-Ibor (1950) included panic attacks and the freudian concept of “Angstneurose”. However, with the development of the concepts of panic disorder and generalized anxiety disorder, with their close association with fear and tension, and prominent autonomic symptoms, our concept of “Angústia” returned to its strict Latin meaning of constraint, like the related medical terms “Angina” and “Angor Pectoris”.

So, as a working definition, our current concept of “Angústia” could be: a special form of intense mental discomfort and restlessness, not necessarily accompanied by autonomic hyperactivity, with the characteristic sensations of constriction, pressure, heaviness or void, mainly in the chest, epigastrium or throat. Pending further studies, this cluster of symptoms is more frequently observed in patients with depression than panic disorder. Its intensity generally accompanies the diurnal variation of both typical and atypical depressive syndromes, and its presence in dysthymia has not been determined.

Why should we bother with such psychopathological details? Because of their potential usefulness in the discrimination between depressive and anxiety states, and the possibility that improvement in “angústia” is the early predictor of response to antidepressant treatment of patients with major depression, detected under the less specific word “anxiety”.

Another typical problem in South America, which presumably also occurs in other parts of the world, derives from the stage of economic development of the region: psychiatrists and primary care physicians often rely on the message of local “opinion leaders” and “foreign experts”, espe-
cially during the introduction of new drugs. However, our experienced clinicians are only asked to take part in the final stages of testing such drugs, largely to become acquainted with their effects in multicenter trials, and the experts are usually engaged in industry-sponsored programs.

We all rely on double-blind, controlled trials, but we must keep in mind that their funding remains heavily dependent on marketing strategies, or they are sponsored by the government of wealthy countries, with their own realities and idiosyncrasies. Obviously, such trials do not address all relevant clinical or scientific observations. For instance, we had to run a controlled trial of clomipramine in panic disorder with funds raised from donations, to test a long-lasting regional experience that it is a more potent and a better reference treatment for panic/agoraphobia than imipramine (Gentil et al., 1993). It is noteworthy that clomipramine is not available for the treatment of panic in the USA.

A recent danger of consolidating partial truths from insufficient evidence comes from the inadequate use of metaanalysis. Indeed, to be useful metaanalysis requires a large pool of sound information. A 50% reduction in rating scores (e.g., Angst, Scheidegger and Stabl, 1993) may suggest efficacy, but is too little for conditions fully responding to effective treatments (Hellerstein et al., 1993).

These concerns are particularly relevant for dysthymia, as there are evidences that it may have a poorer prognosis than major depression (e.g., 39% versus 97% recovery rates in a 2-year follow-up study, respectively; Keller and Lavoni, 1984), and contributes to higher rates of relapse of major depression in patients with double-depression (Keller et al., 1983). How much of the poor response of dysthymic patients is due to the presumption of characterological depression, and a consequently less effective treatment approach is unknown.

MAO inhibitors, such as phenelzine, have a long-lasting tradition of efficacy in “neurotic” and “atypical” depression. Tranclaypramine was recently proven effective in imipramine-resistant recurrent anergic bipolar depression (Thase et al., 1992). Their prescription, however, is beyond the competence of less trained specialists and primary care physicians, and cannot be recommended for primary care.

The role of reversible MAOIs inhibitors and other compounds in dysthymia is currently under investigation.

REFERENCES


Lewis A (1979): Problems presented by the ambiguous word “anxiety” as used in psychopathology. In: The later papers of Sir Aubrey Lewis, Oxford University Press, London: 72-88


THE NEUROENDOCRINOLOGY OF DYSTHYMIA

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Affective disorders are highly prevalent and treatable. However, it has been estimated that less than half of patients with affective disorders seek treatment or are specifically treated. The spectrum of affective disorders covers various conditions of varying chronicity and severity, such as dysthymia, unipolar depression, and bipolar disorder. Both from a clinical as well as from a research perspective, it is easier to assess and to investigate the more severe and acute forms of affective disorder. On the other hand, the more chronic forms of mood disorders, such as dysthymia, have a high prevalence, estimated to be approximately 7%, tend to be underdiagnosed and remain mostly untreated, particularly when there is co-morbidity with medical or neurological disorders.

Neuroendocrine studies have been a fertile area of investigation in affective disorders for a variety of reasons: (1) There is an important endocrine component in the response to stress. As stress triggers and worsens affective symptoms, it is reasonable to study stress hormones in mood disorders. (2) Thyroid hormone deficiency can cause dysthymia and depression. Thyroid hormone augmentation is clinically efficacious in the treatment of depression. It has therefore been hypothesized that alterations in thyroid hormones might contribute to depression. (3) Neuroendocrine parameters are measurable in peripheral blood and give us a perspective into potential central nervous system abnormalities that cannot be directly assessed in vivo.

One can consider neuroendocrine dysregulation in affective disorders in several ways: (1) as epiphenomena of the stress of the illness; (2) as potential markers for primary neurotransmitter defects; (3) as intermediaries that confer clinical and biochemical manifestations (e.g. CRH, cortisol, neuroactive steroids, thyroid hormones etc.); (4) as primary defects that confer susceptibility to
depression; (5) as potential diagnostic markers; and (6) as markers for alterations in a complex, redundantly regulated stress system in a disorder that can be precipitated by stress, and whose principal clinical manifestations resemble a sustained version of what some individuals experience transiently under severe duress.

While endocrine alterations in depression have been exhaustively studied much less is known about the specific endocrinology of dysthymia. As an illustration of this point, I should point out that there have been thousands papers published on just one endocrine test (the dexamethasone suppression test - DST) in depression. In contrast a thirty year MEDLINE search shows only 10 papers on neuroendocrine aspects of dysthymia.

We will review current research in the endocrinology of depression, present the findings on dysthymia, and propose new endocrine approaches for the study of dysthymia. We will focus on the hypothalamic-pituitary-adrenal (HPA), and on the hypothalamic-pituitary-thyroid (HPT) axes. The reasons for doing so are three fold: (1) alterations in HPA function affect mood, (2) alterations in HPT function also affect mood, and (3) there is a well studied association between affective disorders and those two important endocrine axes. Interestingly, Redeit et al. have shown a molecular basis for the strong interactions between HPA and HPT function. That group has recently identified a hypothalamic corticotropin release-inhibiting factor (CRIF) that inhibits ACTH synthesis and secretion. They show that prepro-TRH-(178-199), a 22-amino acid peptide, inhibits basal and CRH-stimulated ACTH synthesis and secretion in cultured primary anterior pituitary cells. As this peptide is processed from prepro-TRH in vivo, is found in the external zone of the median eminence, and is secreted from hypothalamic slices in vitro, prepro-TRH-(178-199) fulfills the criteria for a physiological CRIF. The significance of TRH and CRIF sharing a common precursor opens new areas of research in the integrated regulation of HPA and HPT and opens up a new area of endocrine investigation in affective disorders (Redeit et al., 1995).

**DOCUMENTATION OF HYPERCORTISOLISM IN DEPRESSION**

Sachar (Sachar et al., 1970), Carroll (Carroll et al., 1976; Carroll et al., 1981), and Rubin (Rubin et al., 1987) have been instrumental in documenting the hypercortisolism of depression in clinical studies. In addition to studies of basal diurnal cortisol secretion in patients with depression, the dexamethasone suppression test had been the standard test in endocrinology to diagnostically evaluate disorders associated with hypercortisolism. The weight of available data suggest that 50% of patients with major depression failed to adequately suppress adrenocortico steroid secretion following conventional oral low dose (1 mg) dexamethasone administration. Because the pituitary was shown in experimental animals to have more dexamethasone binding sites than hippocampal areas thought to mediate glucocorticoid negative feedback upon the hypothalamus, the locus of hypercortisolism in depression was thought to reside both within the pituitary and centrally (Kathol et al., 1989). Unfortunately, the dexamethasone suppression test is relatively ineffective in distinguishing chronic from acute hypercortisolism, in detecting hyperresponsiveness of the HPA axis during transient periods of eu cortisolism, or in distinguishing pituitary from hypothalamic abnormalities in the axis. Hence, it failed to live up to expectations as either a diagnostic test or a means of substantively elucidating pathophysiological mechanisms of hypercortisolism in depression.
DISCOVERY OF CRH

The discovery of corticotropin-releasing hormone in 1981 (Vale et al., 1981) increased our capacity to study the central component of the HPA axis and to more directly evaluate the functional integrity of pituitary corticotroph cells. Studies in experimental animals showed that CRH not only activated the HPA axis, but also central administration also set into motion a variety of physiological and behavioral responses adaptive during stressful situations and maladaptively altered in patients with major depression (Britton et al., 1982; Cole et al., 1987; Glowa et al., 1992; Rabin et al., 1988; Rivier et al., 1986; Rivier and Vale, 1984; Sirinathsinghji et al., 1983; Sutton et al., 1982; Swerdlow et al., 1986). These effects included both enhancement of fear-related behaviors and inhibition of vegetative functions subserving food intake, sexual function, and sleep. Thus, CRH may be involved, not only in the hypercortisolism of depression, but also in aspects of its clinical phenomenology.

CRH IN MAJOR DEPRESSION

The studies by Gold and Chrousos (Gold et al., 1984), Nemeroff (Nemeroff et al., 1988; Nemeroff et al., 1984), and Holsboer (Holsboer et al., 1984) showed that HPA activation in melancholic major depression is caused by increased hypothalamic production of CRH. Gold, Chrousos et al. implicated CRH in the hypercortisolism of depression utilizing assessment of pituitary-adrenal responses to synthetic ovine CRH (Gold et al., 1984), and subsequently explored the integrity of the HPA axis in depression using a multiplicity of methodologies, including the administration of the glucocorticoid antagonist RU 486, the infusion of arginine vasopressin, the continuous infusion of CRH, and the measurement of CSF CRH via continuous lumbar drainage for thirty hours (Chrousos et al., 1985; Kling et al., 1994). Elevated CSF CRH levels in depression were reported by Nemeroff et al. (Nemeroff et al., 1984). That group also showed that the cerebral cortex of suicide victims from various causes contained a significantly reduced number of CRH receptors post-mortem, which may represent a compensatory response to high endogenous levels of CRH (Nemeroff et al., 1988). Holsboer et al. (Holsboer et al., 1984) replicated the finding that patients with depression exhibited evidence of a pituitary corticotroph cell that was appropriately restrained by hypercortisolism.

THYROID HORMONE ALTERATIONS

Thyroid hormone function affects behavior in humans: hyper- and hypothyroidism can induce disturbances of mood and intellectual function (in severe cases even psychosis can be mimicked). On the other hand affective disorders are associated with alterations of peripheral thyroid hormone metabolism. Approximately 10% of depressed patients have subclinical hypothyroidism and another 35% have a blunted TSH response to TRH. There are reports of positive correlation between elevated T4 and the speed of response to antidepressant drugs. Rapid cycling patients were have a comparably high incidence (up to 50%) of mild subclinical hypothyroidism (Whybrow, 1994;
Whybrow and Hurwitz, 1976). There is extensive literature documenting an association between abnormalities of the hypothalamic-pituitary-thyroid axis and disorders of mood. However, the specific abnormality in thyroid functioning associated with primary affective disorder remains poorly understood (Joffe, 1990).

**RESEARCH IN THE NEUROENDOCRINOLOGY OF DYSTHYMIA**

The available studies on dysthymia show that in contrast to major depression the endocrine findings are much more subtle. Szadoczky et al. have reported alterations in DST suppression and TSH responses to CRH in dysthymia. Those findings occurred in individuals with early onset dysthymia, but not in those with late-onset dysthymia (Szadoczky et al., 1994). Those data seem to indicate that endocrine findings might be a function of chronicity. In a study of biochemical correlates of treatment response in dysthymia, Ravindran et al. found that treatment responders had lower urinary 5-hydroxyindoleacetic acid (5-HIAA) levels prior to treatment. Following treatment, urinary 5-HIAA tended to be decreased in nonresponders and increased in responders. Additionally, metanephrine levels were lower and 6-sulphatoxymelatonin levels were higher in responders prior to treatment (Ravindran et al., 1994a). In dysthymic patients, higher pretreatment plasma cortisol levels following dexamethasone were also associated with a positive treatment response to fluoxetine (Ravindran et al., 1994b). These data support the view that there is a biological substrate for certain subgroups of dysthymia, possibly involving serotonergic systems and HPA function.

Rihmer and Szadoczky have conducted an elegant study of HPT and HPA function in dysthymia. The authors used Akiskal’s criteria of subaffective dysthymia (SDT) and character-spectrum disorder (CSD) and investigated the dexamethasone suppression test (DST) in 18 patients with SDT and in 30 patients with CSD. TRH-TSH test was also investigated in smaller subsamples of the patients (N = 8, and N = 7, respectively). Fifty percent of the patients with SDT showed abnormal DST and TRH-TSH test results respectively, while the figures in the CSD patients were 7% and 0%. These findings suggest that SDT is a clinically diagnosable and biologically distinct subgroup within the broader category of early-onset primary dysthymia, which represents a symptomatically milder version of primary affective disorder. The fact that the endocrine alterations of dysthymia are more subtle than those found in major depression is evidenced by the findings of Leake et al. that the cortisol response to hCRH was higher in depression than in dysthymia (Leake et al., 1989).

**EVIDENCE FOR DECREASED HPA ACTIVITY IN SUBTYPES OF AFFECTIVE DISORDER: IMPLICATIONS FOR DYSTHYMIA**

There are two possibilities for the findings of subtle endocrine alterations in dysthymia. One possibility is that the findings in dysthymia are indeed small and that endocrine alterations are not a hallmark of this disorder. Alternatively it is possible that the findings have been so modest because studies in dysthymia have used the same approach as those in major depression and methods.
were used to study hypercortisolism. It is possible that, similarly to patients with forms of atypical depression, dysthymic patients may have a mild form of central adrenal insufficiency. Such a defect cannot be detected by tests designed to study hypersecretion of cortisol, rather than hypoactivity of HPA function.

Our group first became interested in decreased CRH production in states of atypical depression when we studied Cushing’s disease. In a study of adult patients with documented Cushing’s syndrome and 17 hospitalized, matched controls, using standardized structured interviews and tests we showed that during the active phase of Cushing’s syndrome (prior to and/or on admission), 66.7% of all patients reported histories meeting criteria for a psychiatric diagnosis. Atypical depression was the most common diagnosis involving 51.5% (N = 17) of all enrolled patients. Longer duration of Cushing’s syndrome may place them at increased risk of such psychopathology (Dorn et al., 1995). Patients with Cushing’s disease have low CRH CSF levels (Kling et al., 1991). CRH is a peptide that produces arousal (Britton et al., 1982; Cole et al., 1987; Glowa et al., 1992; Rabin et al., 1988; Rivier et al., 1986; Rivier and Vale, 1984; Sirinathsinghji et al., 1983; Sutton et al., 1982; Swerdlow et al., 1986). We therefore hypothesized that the atypical depressive symptoms might be caused by low central levels of CRH. To test this hypothesis we have studied other groups of patients with atypical symptoms.

We conducted studies of HPA function in chronic fatigue syndrome (CFS), a condition marked by lethargy and hypersomnia. Compared to normal, patients demonstrated significantly reduced basal evening glucocorticoid levels (89.0 +/- 8.7 vs. 148.4 +/- 20.3 nmol/L; P < 0.01) and low 24 h urinary free cortisol excretion (122.7 +/- 8.9 vs. 203.1 +/- 10.7 nmol/24 h; P < 0.0002), but elevated basal evening ACTH concentrations. There was increased adrenocortical sensitivity to ACTH, but a reduced maximal response. Patients showed attenuated net integrated ACTH responses to oCRH (128.0 +/- 26.4 vs. 225.4 +/- 34.5 pmol/L/min; P = 0.04). Although we cannot definitively account for the etiology of the mild glucocorticoid deficiency seen in chronic fatigue syndrome patients, the enhanced adrenocortical sensitivity to exogenous ACTH and blunted ACTH responses to oCRH are incompatible with a primary adrenal insufficiency. A pituitary source is also unlikely, since basal evening plasma ACTH concentrations were elevated. Hence, the data are most compatible with a mild central adrenal insufficiency secondary to either a deficiency of CRH or some other central stimulus to the pituitary-adrenal axis (Demitrack et al., 1991).

We have studied other patient groups with atypical depressive symptoms and similarly, we show evidence for a mild form of central adrenal insufficiency.

We now propose that the pathophysiology of dysthymia might involve a mild central dysregulation of HPA function. Unfortunately, current approaches to endocrine investigation of HPA function are designed to highlight hyperfunction of this axis. We are now developing and validating new methods of endocrine research that permit an accurate assessment of low HPA activity. That is a methodological challenge as there is a very narrow range between the normal curves and the detection limit of our assays. Thus, new approaches are currently being validated in our lab. Those include deconvolution with assessment of kinetic parameters of endogenous hormones, rapid sampling for the assessment of subtle variations in ultradian pulsatility of HPA hormones, and HPA responsiveness to a variety of stressors.

Traditionally, clinical endocrine assessments have relied on the measurement of hormone concentrations in peripheral blood. That approach can be successful if there are substantial differences
in the groups studied, especially in the assessment of increased endocrine function. The assessment of decreased endocrine function is less straightforward for two reasons: 1) low range between normal and detection limit, and 2) individual variation in the determinants of hormone plasma concentrations. The understanding of this second point is crucial for the design of paradigms capable of accurately assessing an endocrine system, and for the detection of significant differences between normal and abnormally low endocrine function within the narrow range between detection limit and normal function.

The concentration of a hormone in plasma is a function of four events. 1) The secretion of the hormone into the blood stream (also known as instantaneous secretion rate or ISR). 2) The fractional rate constants which describe the movement of the hormone into and out of various body compartments (also known as distribution rates). Those rates consist of the rate by which intravascular hormone goes to extravascular compartment(s), and the rate by which extravascular hormone returns to the intravascular compartment. 3) The volume of distribution (or VD), and 4) the rates of hormone metabolism, also known as metabolic clearance rates or MCR. Each of these elements varies considerably among individuals. Consequently, variations in hormone concentrations are the combination of the variation in those four elements. Thus, the assessment of small or subtle differences of hormone concentrations between groups is difficult given the summation of variations in those four parameters.

This process can be conceptualized in the following way: subject A secretes twice as much cortisol as subject B, but metabolizes cortisol twice as rapidly; therefore, the plasma cortisol concentrations of subjects A and B will be same. It can be seen in this simple example that plasma concentrations of a hormone may not reflect great differences in the organization of endocrine regulation, and that the additive effect of variability in the four elements listed above may result in situations when plasma concentrations alone will not reflect in vivo glandular secretory activity, and may not even reveal profound abnormalities in endocrine function. The assessment of endocrine function in the whole organism therefore requires objective, reliable, and valid techniques to appraise secretory activity in vivo.

To circumvent the limitations intrinsic to assessing plasma concentrations of hormones, it is necessary to use more sophisticated methodologies, such as deconvolution. Deconvolution is the mathematical method by which ISR are ascertained, based on a time series of hormone concentrations. That is accomplished by previously determining the distribution rates, volume of distribution, and MCR. With that information it is then mathematically feasible to use concentration values to derive ISR. Deconvolution permits the accurate assessment of in vivo glandular secretory activity. It might be argued that what is important in endocrine assessments are just the concentrations of an informational substance, because that is what the target cell will be exposed to.

That is erroneous for two reasons. 1) An important element of hormone clearance is binding to functional receptors, leading on the one hand to increased second messenger activity and increased biological action. On the other hand, hormone-receptor binding is followed by the internalization and degradation of the hormone-receptor complex, leading to disappearance of the hormone from plasma. In most hormonal systems, increased secretion accompanied by fast extraction by the target organs, may result in increased biological activity of a hormone, without a necessary significant increase in plasma concentrations. 2) Furthermore, in neuroendocrinology research, the endocrine secretory signal is a better reflection of upstream events; e.g., ISR of ACTH by the pituitary are a
more accurate reflection of hypothalamic CRH activity than the plasma concentration of ACTH, which is also a reflection of peripheral events, such as distribution rates and MCR.

The use deconvolution to assess ISR has methodological and practical limitations. Briefly, the accuracy of deconvolution is limited by the accuracy of the estimation of the parameters needed to ascertain ISR. Those parameters are the time series of hormone concentrations, as well as $K_e$, $K_{s}$, $K_{y}$, and $V_D$ (Polonsky et al., 1986). Errors in hormone concentration determination are related to the precise timing of sampling, storage conditions, and assay errors. Those errors are intrinsic to any endocrine study and have been shown, in most cases, to be under 10%. The assessment of $K_e$, $K_{s}$, $K_{y}$, and $V_D$ is more methodologically complex. Basically, three different approaches have been used to accomplish that. They include: 1) radiolabeled tracer; 2) no tracer, using rapid sampling and computer modeling to estimate decay parameters based on the sum of all endogenous downshifts in concentration values; 3) cold tracer as a bolus injection.

Each of those approaches has its own advantages and pitfalls. We opted for the third approach (see appendix for detailed methodology and rationale). In our estimation this approach is not as invasive as using radiolabeled tracer, but it is more precise than methods that do not rely on individual determination of kinetic parameters. Moreover, it permits the determination of the ISR of more than one hormone in the same sample, which is not feasible with the use of the radiolabeled tracer method.

We will describe three clinical research situations which exemplify how the assessment of ISR has proven essential to clarify pathophysiology. In non-insulin dependent diabetes mellitus (NIDDM), several studies had failed to detect a significant difference from normal values in insulin levels during meals. However, a detailed deconvolution study by Polonsky et al. showed that patients with NIDDM have a significant reduction in instantaneous insulin secretion rates during meals (Polonsky et al., 1988). A second example of the value of deconvolution was recently shown by Herman et al. (Herman et al., 1994).

Those authors used deconvolution to unravel the basic pathogenetic mechanism of MODY in the RW pedigrees. MODY (maturity-onset diabetes of the young) is associated with polymorphic DNA markers on chromosome 2q in that pedigree. Those authors found that in nondoniabetic genetic marker (+) RW individuals, there was no abnormality in insulin sensitivity or in pancreatic β-cell hormone concentrations in response to an intravenous glucose challenge. However, the use of deconvolution unmasked a 49% decrease in insulin ISR in nondoniabetic genetic marker (+) RW individuals as compared to nondoniabetic genetic marker (-) RW individuals or healthy controls. This finding strongly suggests that, contrary to what was previously hypothesized as the pathogenetic basis of MODY, it is deranged and deficient insulin secretion rates, and not insulin resistance, that appears to be the predisposing factor in MODY, at least in the RW pedigree. In relation to our own work, Siever & Davis (Siever and Davis, 1985), as well as our own group, had hypothesized that depression was associated with hyperactivity of the sympathetic system; however, we and others found that norepinephrine levels appeared normal in depressed patients. When deconvolution techniques were used, it was possible to demonstrate that in depression there was a significant increase in norepinephrine spillover into arterial plasma.

These three situations illustrate the fact that both conceptually as well as clinically, despite the fact that plasma concentrations of a hormone (or informational substance) may not be statistically different in controls and in a disease state, profound abnormalities in endocrine functioning
can be demonstrated with the use of frequent sampling, rigorously controlled study conditions, and detailed statistical analyses, including the use of techniques such as deconvolution to ascertain ISR.

In their Endocrinology editorial Veldhuis & Johnson (Veldhuis, 1990) commented on the use of ISR in endocrine research. They stated that “The essence of endocrinology is an investigation of the regulation of endocrine glandular secretion”. Such work is increasingly dependent on molecular, organellar, cellular, tissue, and whole organism experiments.

Molecular tools have permitted the evaluation of glandular secretion at the level of regulation of gene expression. The use of state-of-the-art specialized biophysical and mathematical techniques for evaluating in vivo hormone secretion by numerical (deconvolution) approaches has allowed non-invasive reconstruction of the time domain of endogenous glandular secretory activity. We predict that considerable progress will be achieved in our field by a combination of detailed assessments of glandular activity in vivo and the study of the regulation of endocrine function at the molecular level.

CONCLUDING REMARKS

We have reviewed the evidence that dysthymia may be associated with specific endocrine alterations. Few groups are dedicated to this task at present, even though dysthymia is highly prevalent and can substantially contribute to the morbidity of medical and neurological disorders. The high incidence of dysthymia is high: at a rate of 7% prevalence, one can estimate that over 40 million individuals in the Unites States and Western Europe have had dysthymia. New research is truly needed to elucidate the pathogenesis and pathophysiology of dysthymia, hopefully leading to more effective treatments. We propose that dysthymia is associated with mild hypofunction of the HPA axis and by decreased central production of the arousing producing neuropeptide CRH. We are now developing new endocrine approaches to test this hypothesis and are conducting pilot studies on patients with dysthymia and depression, during the symptomatic phase of their disorders as well as during remission.

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MOLECULAR MECHANISMS OF THE STRESS RESPONSE AND THEIR ROLE IN THE PATHOGENESIS OF DYSTHYMIA

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ABSTRACT

The response to stress is essential for survival. The organism requires for its existence a state of metabolic equilibrium or homeostasis. Stressors originating outside the organism, threaten homeostasis and survival. In order to survive all living cells have developed biochemical and molecular mechanisms to cope with stress at the cellular (Wong et al., 1992), systemic (Chrousos et al., 1985), and behavioral levels (Sutton et al., 1982; Swerdlow et al., 1986). The complex repertoire of adaptive responses against stress has a molecular substrate. We are currently developing an understanding of that molecular substrate with an ultimate goal of developing more effective treatment strategies for patients with stress-related disorders.

ARE MOOD DISORDERS STRESS-RELATED DISORDERS?

It is well known that stress can precipitate episodes of mood disorders. Moreover, symptoms of mood disorders cause stress. The question we ask now is whether there is a more causal relationship between stress-responsive neuroendocrine systems and affective disorders. We have attempted to propose a model that accommodates the clinical observation that chronic stress early in life in vulnerable persons predisposes them to affective disorders with contemporary observations of the potential consequences of repeated central nervous system exposure to effectors of the stress response. This model accords with current clinical judgment that major depression is best treated with a combination of psychopharmacologic agents and psychotherapy. Our laboratory has shown that various classes of antidepressants share a common final effect, which is to downregulate the levels of expression of the gene encoding for CRH in the paraventricular nucleus of the hypothalamus (Brady et al., 1991; Brady et al., 1992). Nevertheless, even though psychopharmacologic intervention may be required to resolve an active episode of major depression and to prevent recurrences, psychotherapy may be equally important to lessen the burden of stress imposed by intense inner conflict and counterproductive defenses (Gold et al., 1988a; Gold et al., 1988b).
THE MOLECULAR BASIS OF THE STRESS RESPONSE

At the most fundamental molecular level the response to stress is mediated via intracellular proteins that are induced when the cell is exposed to physical stress such as heat or noxious chemicals. These proteins are known as heat shock proteins (hsp) and can be induced in mammalian brain by seizures, psychophysiological stress, exercise, (Flanagan et al., 1995) and heat (Fukudo et al., 1995; Skidmore et al., 1995; Wong et al., 1992). However, the relevance of hsps to psychological stress and to affective disorders is unclear at present.

Our laboratory has focused on the expression of genes encoding stress-responsive neuropeptides. We have focused our efforts on the CRH system for several reasons: based on endocrine, post-mortem, as well as CSF data it has been demonstrated that CRH is elevated centrally in depression. The data are not so clear for dysthymia.

CORTICOTROPIN-RELEASING HORMONE

Corticotropin-releasing hormone (CRH) is a 41 aminoacid peptide neurohormone that is synthesized in hypothalamic and extrahypothalamic sites (Vale et al., 1981). CRH receptors have been recently cloned by Vale et al. (Chen et al., 1993; Perrin et al., 1995). We have conducted a detailed localization study on CRH receptor type 1 gene expression in adult rat brain (Wong et al., 1994). Autoradiography of CRH receptor mRNA in adult rat brain showed hybridization to several discrete brain regions. A strong autoradiographic signal was observed over the pituitary, the granule cell layer of the dentate gyrus and pyramidal cell layer of the hippocampus, pyriform cortex and cerebral cortex areas. Other areas that showed hybridization include: olfactory bulb, choroid plexus, nucleus of the lateral olfactory tract, paraventricular nucleus (hypothalamus), ventromedial nucleus (hypothalamus), arcuate nucleus (hypothalamus), thalamus; amygdala, entorhinal area, cerebellar cortex, and inferior colliculus. Control hybridization of adjacent sections with labeled CRH sense riboprobes produced a uniform, low signal, which was barely visible on film. Treatment with excess cold probe (100 x), also used as control, likewise yielded only background hybridization, showing that the localization findings are specific to CRH receptor mRNA.

PROOPIO MELANOCORTIN CORTICOTROPIN-RELEASING HORMONE RESPONSIVE ELEMENT BINDING PROTEIN 1 (PCRH-REB-1)

A major effect of CRH receptor activation is an increase of POMC gene expression. Recently Jin et al. (Jin et al., 1994) identified a core palindromic CRH-responsive element, CTGTGGCCGCAG, (-171/-160) in the POMC promoter (PCRH-RE) and cloned, from CRH-treated pituitary cells, the cDNA encoding PCRH-REB-1, a DNA-binding protein that specifically binds to the PCRH-RE. PCRH-REB-1 seems to be one of a growing number of proteins that function in both transcription and replication. The neuroanatomical identification of the sites of PCRH-REB-1 gene expression in the CNS has not to our knowledge been described. We used a riboprobe generated from the rat
PCRH-REB-1 cDNA to answer the following question: What is the localization of PCRH-REB-1 mRNA in adult rat brain?

Studies were carried out in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the National Institutes of Health. We conducted in situ hybridization histochemistry experiments, using a species-specific, antisense, 32P-labeled PCRH-REB-1 riboprobe, hybridized to brain and pituitary slices, from virus- and antibody-free, non-stressed Sprague Dawley rats (Harlan, Indianapolis, IN). Excess cold probe (100 x) and sense probe were used as controls.

Autoradiography of PCRH-REB-1 mRNA in adult rat brain showed hybridization to several discrete brain regions. Control hybridization with labeled CRH sense riboprobes produced a uniform, low signal, which was barely visible on film. Treatment with excess cold probe (100 x), also used as control, likewise yielded only background hybridization.

Forebrain: telencephalic structures were predominant among the forebrain sites of PCRH-REB-1 mRNA hybridization signal. The signal was localized over cortical layers II, III, and IV. In the hippocampal formation, positively hybridized cells were numerous in the dentate gyrus; the pyramidal cell layer of all subfields of Ammon’s horn had a strong hybridization signal. Expression of PCRH-REB-1 mRNA was detectable throughout all layers of the entorhinal cortex. Among subcortical telencephalic structures, the basal ganglia contained a small density of cells with low hybridization signal. In the limbic region of the telencephalon, PCRH-REB-1 mRNA expression was prominent in the lateral and triangular septal nuclei. Within the amygdaloid complex, moderate to low expression was found over the central, lateral, basolateral, and basomedial nuclei. PCRH-REB-1 mRNA expression in diencephalic cell groups was generally low in the thalamus. In the hypothalamus, signal was generally moderate to low; among neurosecretory structures, hybridization signals were seen over the paraventricular, supraoptic and arcuate nuclei. Brainstem: among the brainstem sites of PCRH-REB-1 mRNA signal were cell groups involved in the processing of somatic sensory information: strong hybridization signals could be seen in the trigeminal sensory structures. Lower levels of labeling were found over the locus coeruleus. In the cerebellum, cells hybridized with the PCRH-REB-1 antisense probe were seen over the Purkinje and granule cell layers of the cerebellar cortex. Pituitary Gland: positive PCRH-REB-1 mRNA signals of moderate intensity were localized over the intermediate and anterior lobe of the pituitary. A moderate PCRH-REB-1 mRNA signal was found over the choroidal plexus of the lateral ventricles.

The LC is unique among brain structures that express PCRH-REB-1 mRNA in that LC CRHR have not been definitively identified (Chen et al., 1993; De Souza et al., 1985; Lovenberg et al., 1995; Perrin et al., 1995; Wong et al., 1994; Wynn et al., 1984). Nevertheless, the LC contains CRH and it is thought to be a particularly important target of CRH. Local iontophoresis of CRH onto the LC increases LC firing, and CRH antagonists applied to the LC decrease norepinephrine and behavioral responses to stressful stimuli (Swiergel et al, 1992; Valentino et al, 1993). Our data showing that PCRH-REB-1 mRNA is localized in LC provide additional support to the concept that the LC may contain a novel CRH receptor subtype that has not yet been identified.

Inflammation and stress stimulate CRH secretion (Cizza et al., 1993; Kakucska et al., 1993), potentially inducing POMC transcription factors. We used virus- and antibody-free animals, which were sacrificed within 45 seconds of being individually removed from cages. Thus, our data are not the result of stress or infection, but represent the constitutive basal pattern of PCRH-REB-1 gene expression in the brain and pituitary.
Figure 1: Localization of proopiomelanocortin-corticotropin-releasing hormone responsive element binding protein (PCRH-REB-1) mRNA in rat cortex, hippocampus, and habenula. Computer enhanced autoradiogram of brain section hybridized with a 35S-labeled rat PCH-REB-1 antisense riboprobe. Purple indicates background, pink/red indicate areas with moderate hybridization signal, and yellow/green represent areas with higher levels of hybridization.
Molecular Mechanism of The Stress Response and Their Role in the Pathogenesis of Dysthymia

POMC transcription is regulated at multiple levels by several informational substances, such as CRH, arginine vasopressin, and interleukin 1. It is not surprising that the POMC gene has various responsive elements that are associated with multiple DNA-binding proteins. Several areas of the POMC gene affect transcription. The core region -171/-160, known as PCRH-RE, was recently identified by Roberts’s group (Jin et al, 1994); the PCRH-RE can increase transcription 5-7 fold and binds PCRH-REB-1. Riegel and colleagues (Riegel et al., 1990) identified region -15/-3, known as the PO-B site, responsible for 70% of the basal POMC transcription rate, and which binds two transcription factors, PO-B and PO-GA (Lu et al., 1993). PO-GA and PCRH-REB-1 are 90% homologous. Loeffler and associates (Boutilier et al., 1995) have identified an AP-1 site in exon 1 of the POMC gene which affects the transcription of a minimal POMC promoter CAT reporter gene construct 6-10 fold, by mechanisms which do not require cFos. Thus, PCRH-REB-1 is only one of many DNA-binding proteins associated with various sites of the POMC gene that are important for transcription.

The gene encoding for PCRH-REB-1 is localized in brain areas known to contain CRH or CRH receptors and which respond to CRH. These findings raise the possibility that PCRH-REB-1 gene expression may result from CRH action. CRH is involved in the pathophysiology of affective disorders diseases (Gold et al., 1984, 1986a, 1986b; Nemeroft et al., 1984; Sternberg et al., 1989); the cloning of three CRH receptor subtypes has led to an intense search for agents that affect CRH function. The evaluation of CRH action and the identification of clinically useful CRH agonists and antagonists would be greatly facilitated by the assessment of an intracellular index of CRH bioactivity. The hypothesis that PCRH-REB-1 may be a marker of cellular responsiveness to CRH should therefore be tested.

CONCLUDING REMARKS

The study of molecules that serve as signal transducers for stress-related hormones is a new frontier for those searching for pathogenetic mechanisms in affective disorders. The genes encoding for those molecules should be useful as candidate genes in genetic studies of affective disorders; moreover, pharmacological agents that affect the functioning of signal-transducing molecules might represent new therapeutic opportunities in depression and dysthymia. Finally, a marker of the cellular responsiveness to CRH should greatly facilitate future studies on the neurobiology of this important hormone that is abnormally regulated in affective disorders. Much work remains to be done in this field.

These new strategies should bring us closer to our goal of identifying at the most fundamental level the biological basis that predisposes individuals to dysthymia.

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THE ROLE OF DOPAMINE IN THE BIOLOGICAL BASIS OF DYSTHYMIA

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ABSTRACT

This paper reviews the recent literature supporting the hypothesis that reduced neurotransmission in the mesolimbic dopamine (DA) system may sustain some of the core and subsidiary symptoms of dysthymia and other depressive conditions, namely anhedonia, lack of interest, lack of drive, lack of concentration, and psychomotor retardation. Experimental evidence indicates that mesolimbic DA mediates the rewarding, motivating and incentive effect of natural and artificial stimuli such as sex, foods, liquids, intracranial self-stimulation, and the drugs of abuse, cocaine and amphetamine.

Conversely, it has been shown that withdrawal from chronic treatment with these drugs is associated with depressive symptomatology and reduced release of DA in the ventral striatum. Similarly, different models of depression such as “behavioral despair”, “learned helplessness” and “chronic mild stress” are associated with reduced DA activity in the limbic system, which is reversed by chronic treatment with antidepressants. Different antidepressants, irrespective of their acute action on the uptake of specific neurotransmitters such as noradrenaline, serotonin and DA, when given chronically have the common property of potentiating those behavioral responses to psychostimulants that are mediated by DA receptors in the limbic areas. The DA hypothesis of depression offers a logical explanation for the antidepressive effect of drugs such as sulpiride and amisulpride, that preferentially block DA autoreceptors and thereby increase DA output.

54
INTRODUCTION

This paper will review recent experimental evidence supporting the crucial role of mesolimbic DA in controlling desire, drive and pleasure; what neuropsychological terminology defines “incentive motivation and reward”. Moreover, the involvement of mesolimbic DA both in the symptomatology of animal models of depression and in the mechanism of action of classic and new antidepressant treatments will be analyzed.

Dopamine, Desire, Drive, Pleasure

Compelling evidence indicates that dopaminergic neurons originating in the ventro-tegmental area (VTA) and innervating, inter alia, the nucleus accumbens, play a crucial role in incentive motivation and reward (Wise, 1989; Fibiger and Phillips, 1987; Blackburn et al., 1992). Indeed, physiological stimuli such as sex, food and water, or artificial stimuli, such as drugs and electrical stimuli that produce motivation and reward, also stimulate the release of DA in the nucleus accumbens. Conversely, the reward produced by these stimuli is suppressed by the lesion of DA neurons or by the blockade of DA receptors in this area.

Intracranial Self-Stimulation

The reward of intracranial self-stimulation (ICSS) obtained from electrodes positioned in the medial forebrain bundle or in the VTA is reduced after 6-OH-DA-induced lesions of the mesolimbic DA neurons or by the intra accumbens administration of DA receptor antagonists (Fouriezos et al., 1978; Fibiger et al., 1974). Conversely, different drugs that produce reward, such as cocaine, amphetamine, morphine and nicotine, increase the rewarding consequences of ICSSASIC (Frank et al., 1992) and increase DA release in the nucleus accumbens (Di Chiara and Imperato, 1988). Finally, DA synthesis metabolism and release in the nucleus accumbens are increased during VTA self-stimulation, and DA output is correlated with the rate and intensity of self-stimulation (Fiorino et al., 1993).

Self-Administration of Drugs

Rats will work, e.g. performing lever press, for the self-administration of the same drugs that are abused by man, such as cocaine, morphine/ heroin, amphetamine and alcohol, indicating that these drugs are rewarding for the experimental animal as well (Pettit et al., 1991; Shaham and Stewart, 1995; Yokel and Wise, 1976; Weiss et al., 1993). However, while convincing evidence implicates mesolimbic DA, and more specifically meso-accumbens DA, in mediating the rewarding effect of cocaine and amphetamine, the role of DA in the rewarding effect of alcohol and opioids is debated (see Figure 1). Thus, the 6-OH-DA-induced lesion of DA terminals in the nucleus accumbens (Roberts and Koob, 1982; Lyness et al., 1979), has been shown to suppress self-administration of cocaine and amphetamine. The blockade of either D, or D, DA receptors in the nucleus accumbens also suppresses cocaine and amphetamine self-administration (Roberts et al., 1980, 1984; Yokel and Wise, 1975). Before the blockade is established, self-administration of these drugs increases, reflecting the animal’s attempt to overcome the reduced reward (Roberts et al., 1980, 1984; Yokel and Wise, 1975; Koob et al., 1987).

Finally, microdialysis studies have shown that intravenous self-administration of cocaine, amphetamine, morphine and oral self-administration of alcohol are associated with an increased DA
output in the nucleus accumbens (Pettit and Justice, 1991, 1983; Weiss et al., 1993). These results suggest that the rewards produced by the ICSS or by drugs of abuse travel along the dopaminergic fibers of the meso-accumbens pathway.

**NATURAL STIMULI**

*Sexual Behavior*

Mesolimbic, incerto-hypothalamic and tuberoinfundibular dopaminergic systems control different aspects of sexual behavior in male rats. Mesolimbic DA seems to be involved mainly in the control of anticipatory (preparatory, appetite) aspects of male sexual behavior rather than in the consummatory aspects (Melis and Arigolas, 1995).

In fact, disruption of DA transmission in the nucleus accumbens induced by the 6-OH-DA-neurotoxine or by DA receptor blockade impairs the preputatory investigation of the female by the male, delays the initiation of mounts, decreases the chasing by the male rat of the receptive female, and the willingness of the male rat to work, e.g. by lever pressing, to gain access to a receptive female. Moreover, the blockade of DA transmission reduces in the male rat the condi-
tioned preference for a place where it previously copulated, or in which a receptive female had been placed (Pfaus and Phillips, 1991). Much higher doses of DA antagonists are needed to reduce the consummatory aspects of copulatory behavior (Agmo and Fernandez, 1989).

Microdialysis studies have shown that DA release in the nucleus accumbens can be elicited in the male rat by the presentation of a receptive inaccessible female behind a screen or by exposure to an environment containing odors of a previous copulation (Damsma et al., 1992). However, changes in DA output are not confined to the preparatory phase of copulatory behavior, but DA release in the nucleus accumbens, as well as in the dorsal striatum and in the medial preoptic area, further increases during the consummatory phase of sexual behavior, consisting of multiple series of mounts and penile intromissions; each series culminating in one ejaculation (Pfaus et al., 1990; Pleim et al., 1990). However, in spite of the increased DA output, copulatory behavior is rather insensitive to treatments that suppress DA neurotransmission in the nucleus accumbens, suggesting that the increased DA conveys the reward, but is not critically involved in the stereotypic motor aspects of the copulatory behavior (Melis and Argiolas, 1995; Agmo and Fernandez, 1989).

More recently, Agmo and Berenfeld, have shown that the rewarding effect of ejaculation, as measured by the conditioned place preference procedure, is more dependent on opioids than on DA, since it is suppressed by naloxone, but not by DA receptor antagonists (Agmo and Berenfeld, 1990).

**Food and Sweets**

When a rat is exposed to stimuli that anticipate the delivery of a meal, there is a conditioned increase in DA in the nucleus accumbens that coincides with the display of preparatory responses. The preparatory responses are suppressed by the disruption of DA neurotransmission (Blackburn et al., 1992). DA release also increases following the intake of particularly palatable fluids, such as a sucrose solution. Periodic presentation of food to food-deprived rats produces a behavioral stimulation and an increased release of DA in the nucleus accumbens similarly to that produced by cocaine or amphetamine. DA release is also increased by lever pressing for food reinforcement (Blackburn et al., 1992; McCullough and Salamone, 1992; Hernandez and Hoebel, 1988). Motor response in both cases is reduced both by 6-OH-DA-induced lesion of DA innervation and by the blockade of DA receptors in the nucleus accumbens. As in the case of copulatory behavior, the consummatory act of feeding itself also seems to be relatively independent of DA involvement, except for the initiation of feeding which is delayed by DA receptor antagonists (Blackburn et al., 1992). Recent experiments from our laboratory have shown that DA output in the nucleus accumbens increases during the first part of the night when the rat, which is a nocturnal animal, displays most of its motivated behaviors, including eating, drinking and sexual behavior (Gessa et al., ms. in preparation).

**DEPRESSION AFTER WITHDRAWAL FROM CHRONIC PSYCHOSTIMULANTS**

Following discontinuation of chronic use of cocaine or amphetamine, humans develop a withdrawal syndrome characterized by a depressive symptomatology including lethargy, fatigue, dysphoria and a depressed mood (Weddington et al., 1990; Gawin and Kleber, 1986; Watson, 1972; Schildkraut et al., 1971; Watson et al., 1992). Rats too, on withdrawal from chronic administration of these drugs show a behavioral syndrome characterized by hypovigilance, decreased sensitivity to
the rewarding effect of ICSS and conditioned place aversion (Markou and Koob, 1991; Mucha, 1987; Pilcher and Stolorz, 1976). A number of studies have shown that withdrawal from chronic cocaine and amphetamine is associated with a decreased release of DA in the ventral striatum, suggesting that a decrease in DA neurotransmission may be responsible for the subjective aversive symptoms associated with withdrawal from these drugs (Rossetti et al., 1992; Robertson et al., 1991; Acquas et al., 1991; Acquas and Di Chiara, 1992).

ANIMAL MODELS OF DEPRESSION

Long-term exposure of rats to mild stress causes a decreased sensitivity to reward, which has been suggested to be homologous to anhedonia, a specific symptom of depression. This behavioral effect in rats is associated with a decreased responsiveness of D1/D2 DA receptors in the nucleus accumbens. Both the behavioral response and the decreased sensitivity of DA receptors are reversed by chronic treatment with classic and new antidepressants (Willner, 1995).

Interestingly, in the mild stress-induced model, postsynaptic DA receptors are hypoactive while DA release is not reduced. Instead, in the psychostimulant-withdrawal model there is an inhibition of DA output associated with supersensitivity of postsynaptic DA receptors. These findings suggest that the reduction of DA transmission might be produced via different mechanisms. The presence of a hyper or hypoactivity of postsynaptic DA receptors might explain the presence or absence of psychotic symptoms, such as delusions and agitation, in different depressive disorders and the facility or resistance to shifts from depression to mania.

In the learned helplessness model, the animal pre-exposed to an inescapable or uncontrolled aversive event, usually an electric shock, becomes unable to escape from a controllable aversive event, remaining passive, immobile and showing various somatic disturbances. In the behavioral despair test, a state of immobility is produced by forcing the rat to swim in a confined space. The immobility in the learned helplessness model is reversed and that in the behavioral despair model is delayed by chronic treatment with newer and older antidepressants or by ECT (Porsolt, 1981; Gambarana et al., 1995). Learned helplessness and behavioral despair have been shown to be associated with depletion of DA content and reduction in DA output in the nucleus accumbens, respectively (Willner, 1983; Rossetti et al., 1993). Moreover, the debilitating consequences of inescapable shock on later escape performance are exacerbated or mimicked by DA receptor blockade (specially D1 blockade) and are antagonized by DA receptor agonists. Similar results have been obtained with DA agonists and antagonists with respect to the immobility in the behavioral despair test.

MESOLIMBIC DA AND ANTidepressants

Antidepressant Treatments and DA

The most obvious objection to the DA hypothesis of depression is that clinically effective antidepressants inhibit serotonin (5-CT) and/or norepinephrine (NE) uptake, but not that of DA. However, experiments aimed at clarifying the apparent contradiction of the fact that, although blockade of SE and NE uptake occurs immediately after acute treatment, the clinical antidepressive effect takes
The Role of Dopamine in the Biological Basis of Dysthymia

place after 2 to 4 weeks of treatment, have offered the strongest support for the DA hypothesis. It was found that a common feature of clinically effective antidepressants, irrespective of their acute effect on NE or SE uptake following chronic treatment, is that they all potentiate DA transmission in the nucleus accumbens. Thus, chronic treatment with different classes of antidepressants (e.g. tricyclic, mianserin, fluoxetine etc.) potentiates the psychostimulant effect of direct and indirect DA agonists, such as apomorphine, amphetamine, cocaine, etc. (Serra et al., 1992). As for the clinical response, this potentiation is produced after chronic but not acute treatment, takes place during the course of treatment and persists long after treatment withdrawal. The potentiation is selective for the behavioral responses that are considered to be mediated by D2 receptors in the nucleus accumbens, such as exploratory and rearing activity. In contrast chronic antidepressant treatment does not potentiate DA agonist-induced stereotypies, which are thought to be sustained by activation of the nigrostriatal DA system. Facilitation of DA transmission is produced also by non-pharmacological antidepressant treatments, such as repeated ECS and sleep deprivation. Recent microdialysis experiments have shown that repeated treatment with imipramine and desipramine markedly enhanced cocaine- and amphetamine-induced DA release in the nucleus accumbens, suggesting that these treatments, in addition to producing a postsynaptic facilitation of DA transmission, also modify presynaptic mechanisms controlling DA release, synthesis and inactivation (Rossetti et al., 1991; Nomikos et al., 1991).

CLINICAL CONSIDERATIONS

A common feature of different depressive conditions is the impaired capability to experience “the real pleasure” of anticipating, seeking and consuming sacred or profane desires (sex, food, work, success, etc.) and the lack of energy to overcome the difficulties of everyday life, there is a lack of joy in attaining the goal.

Experimental evidence suggests that what is missing in depressives are the functions that are controlled by mesolimbic DA. Conversely, whenever symptoms of depression can be modeled in experimental animals, they appear to be sustained by a deficit in mesolimbic DA transmission.

The DA hypothesis of depression implies that a deficit in mesolimbic DA transmission is the common neurobiological substrate of the core symptomatology in different depressive conditions irrespective of their diagnostic categorization, including dysthymia disorder, major depressive disorder, drug-induced depression, etc. Focusing on DA does not rule out the role of other neurotransmitters in the pathogenesis of the depressive symptomatology. For example, the very fact that classic and newer antidepressants primarily acting on NE and SE uptake mechanisms do eventually modify DA transmission after chronic treatment indicates the existence of an interplay of different neurotransmitters and suggests that a deficit in DA transmission may not be primitive, but the result of the alteration of other neurotransmitter systems.

A better understanding of how the DA system may be altered by stress, sleep deprivation, drugs, diseases, etc. may offer an explanation for the heterogeneity of depressive disorders, i.e. why some persist monotonously as a way of life, others occur in devastating episodes, others shift between mania and depression. The DA hypothesis of depression offers a logical explanation for the antidepressive effect of drugs such as sulpiride and amisulpride, that preferentially block DA autoreceptors and thereby increase DA output.
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CEREBRAL BLOOD FLOW IN DYSTHYMIA

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Functional brain imaging provides in vivo instantaneous assessments of central neural activity by means of flows or metabolisms that are sensitive and reliable measures of local neuronal functions (Raichle, 1987).

Positron emission tomography (PET) is a high sensitive technique with a level of resolution now reaching less than 3 mm. PET is able to rate the whole or regional cerebral blood flow (CBF) with O15 and a large majority of studies use 18F deoxyglucose to measure cerebral metabolism rates (CMR). It is also adapted to neurotransmitter receptor imaging using radiolabelled ligands that bind to specific neuroreceptors. The expense of the equipment and the radiopharmaceuticals, and the necessity for close proximity to a cyclotron to produce short half lives chemicals are constraints that limit this approach to selective research topics.

Single photon emission computed tomography (SPECT) was initially developed to overcome the limitations of PET. SPECT technology has improved with development of instrumentations and radiopharmaceuticals. SPECT can now also be coupled with receptor binding radiotracers (Kerwin and Pilowsky, 1995). The Radiopharmaceutical compound Xenon 133 has been used for several years. In spite of its qualities, other radiopharmaceuticals like iodine 123, (Iodoamphetamine), HMPAO-Tc99 and more recently ECD-Tc99, have been developed providing higher levels of energy that allow better levels of resolution, now reaching 8 mm. SPECT is available in many medical imaging departments. This technique may be more appropriate for routine clinical application in a variety of medical conditions.

Progress towards understanding pathophysiology of psychiatric disorders may certainly be expected with such a sophisticated technology provided by nuclear medicine. Nevertheless clinicians have to be warned of methodological issues in observing in vivo brain activity. There is a growing body of literature in this area to delineate factors affecting cerebral blood flow or metabolism that need to be controlled prior to interpretation. Age (Hagstadius and Risberg, 1983), gender (Gur et al., 1995; Rodriguez et al., 1988; Warach et al., 1987), sensory, sensitive, motor and cognitive
activity (Phelps and Mazziotta, 1985), mental task during acquisition (Post et al., 1987; Ingvar, 1994), psychotropic drugs (Passero et al., 1995), and medical condition all markedly modify brain imaging patterns.

During the past twenty years, functional brain imaging techniques have been applied to the field of affective disorders. Since there is compelling evidence for a biological basis to major affective disorders, most of the studies have focused on primary major depression. Only a minority of studies have examined patients with dysthymia. Secondary affective disorders related to brain lesions also remain under-assessed.

The main limitation of brain imaging studies in dysthymia is based upon persisting uncertainty about its nosological status. Heterogeneous clinical or psychopathological aspects make it difficult to differentiate between mood or personality disorders (Klein et al., 1995; Freeman, 1994). The diversity of illness duration, past histories of medication and medical disorders often associated dissuaded investigators from starting studies that until now aimed to determine common patterns of a disorder within patients with identical nosological criteria.

There are now evidences to admit there is an overlapping between dysthymia and major depressive illness (Keller and Lavori, 1984). Recent studies have suggested that dysthymia share some biological markers (Akiskal, 1994; Howland and Thase, 1991; Poirier, 1994) and some subgroup of dysthymic patients respond effectively to psychotropic agents that are effective in depression (Akiskal, 1992; Bakish et al., 1994; Kocsis et al., 1995). Those findings emphasise the necessity to conduct studies that point out prognostic and therapeutic rather than diagnostic issues.

Thus, reviewing studies on affective disorders may be of interest to specify the appropriate questions that clinicians must address to nuclear medicine in the field of dysthymia.

**BRAIN IMAGING STUDIES IN PRIMARY MAJOR DEPRESSION**

Initial studies often produced conflicting results; above all, these discrepancies have emphasised the methodological issues that later studies are striving to consider. Technical advances in the computerisation and spatial resolution of emission imaging and standardisation of the techniques may undoubtedly improve the quality of data and interpretation of the results. However under-documented or unspecified selection criteria of such a multiple-facet disorder may explain most controversies.

When compared with controls, patients experiencing a depressive episodes showed global and regional decrease in cerebral blood flow and metabolism; only a minority described increases (Silverskiöld et al., 1987). In spite of widely distributed topographic modifications, the most common abnormalities observed include frontal (Buchsbaum et al., 1986; Baxter et al., 1985; Guze et al., 1991; Martinot et al., 1990; Post et al., 1987; Bench et al., 1992; Sackeim et al., 1990; Mayberg et al., 1994; Austin et al., 1992; Francois et al., 1995; Yazici et al., 1992) temporal (Post et al., 1987; Sackeim et al., 1990; Mayberg et al., 1994; Austin et al., 1992; Amsterdam and Mozley, 1992) and less consistently other limbic (Mayberg et al., 1994; Post et al., 1987; George et al., 1993; Schneider et al., 1996) CBF and CMR decrease.

Studies assessing patients both on the depressed state and in the recovered state reported no
change with recovery or a reversal of some, but not all, abnormalities especially in the frontal areas (Baxter et al., 1989; Drevets 1992, Goodwin et al., 1993). Another common result is the laterisation of the significant decreases of both CBF and CMR to the left hemisphere. Those last data are consistent with findings obtained from other investigations like EEG (Flor-Henry, 1979; Davidson, 1988) or neuropsychology (Kinsbourne, 1988; Tucker, 1988; Wale and Carr, 1990), supporting the hypothesis that affective disorders are associated with right hemisphere function's abnormality (Otto et al., 1987).

Correlations with quantitative clinical measures provide more contradictions albeit recent studies indicated symptomatic specificity related to regional functional deficits. Functional imaging also allowed distinctions between subgroups of depression; different patterns have been described in bipolar versus unipolar depressions (Baxter et al., 1989; Uytendafoe et al., 1983), endogenous versus non-endogenous depressions (Austin et al., 1992), major depression versus double depression (Thomas et al., 1993). Expectations from these findings could have helpful implications in prognostic and treatment strategy adjustments, however the diversity of standards in brain imaging units hamper replication and validation trials.

BRAIN IMAGING STUDIES IN SECONDARY DEPRESSION

Clinical depression may also be characterized by decreased frontal regional activity when co-occurs with epilepsy (Bromfield et al., 1992), Parkinson disease (Mayberg et al., 1992; Ring et al., 1994), Huntington disease (Mayberg et al., 1992), HIV dementia (Schwartz et al., 1994), Gilles de la Tourette syndrome (Moriarty et al., 1995) systemic lupus erythematosus (Kodama et al., 1995) and frontal dementia (Lucente et al., 1994). Decreased left frontal (Yamaguchi et al., 1992) and temporal regional activity (Pozzilli et al., 1991; Grasso et al., 1994) has been described in post-stroke depression. Methodological issues in this area related to lesions volume multiplicity and topography emphasise the need to superimpose structural brain imaging (CT or MRI) with functional imaging.

BRAIN IMAGING STUDIES IN DYSTHYMIA

The small number of brain imaging studies including patients with dysthymia aimed to compare major depression with a less severe condition that may be intermediary with control subjects. Uytendafoe in 1983 using Xenon inhalation method with a multidetector helmet, noted higher left frontal and lower right posterior cerebral blood flows in patients with major depression compared with controls, these anomalies not being found in patients with minor depression or those with bipolar disorders in the euthymic phase.

Chabrol in 1985 observed with the same technique a reduction in the physiological hyperfrontal pattern which was less pronounced in dysthymic adolescents than in those who presented with major depression. Kuhl in 1985 studied with PET F-deoxyglucose seven patients with depression of whom four were dysthymic. He noted an hypometabolism in the left postero-inferior frontal cortex in all of the patients although he did not record the differences between the two subgroups.
Table 1: Subjects characteristics

<table>
<thead>
<tr>
<th></th>
<th>Major Depress.</th>
<th>Double Depress.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr. of subjects</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Age; mean +/− SD</td>
<td>40.1 + 9.74</td>
<td>37.76 + 9.92</td>
</tr>
<tr>
<td>Gender: Women / Men</td>
<td>9 / 12</td>
<td>12 / 9</td>
</tr>
<tr>
<td>MADRS Score: mean +/− SD</td>
<td>32.62 + 7.65</td>
<td>27.33 + 4.23</td>
</tr>
<tr>
<td>ERD Score: mean +/− SD</td>
<td>25.95 + 8.73</td>
<td>19 + 4.43</td>
</tr>
</tbody>
</table>

Using SPECT with the 99TcHMPAO perfusion technique we studied regional CBF of drug-free depressed consecutive inpatients (Thomas et al., 1993). The aim of our study was to test the hypothesis that in spite of very similar clinical features at the time of hospital admission, patients may disclose different cerebral activity patterns according to their nosological status. This hypothesis is based upon evidences of different pathogenic mechanisms involved (Akiskal) as reflected by clinical history and evolution.

21 patients with the diagnosis of major depression and 21 with double depression - dysthymia with a super-imposed major depressive episode (Keller) - all of them with the Montgomery and Asberg depression rating scale (MADRS) score greater than 20 were included in the study after giving written informed consent. Severity of depression was assessed with the MADRS and the Widlocher and Jouvent’s psychomotor retardation scale.

Patients showed neither psychotic characteristics nor other diagnostic on DSM-III-r axe 1 (see subjects characteristics Table 1). The mean length of time that the dysthymic disorder had been present was 6.25 years the range being from 3 to 12 years. Clinical examination, EEG findings and the results of laboratory tests were within normal limits.

Table 2: Regional cerebral HMPAO uptake indexes; mean +/− SD

<table>
<thead>
<tr>
<th>Region</th>
<th>Major Dep.</th>
<th>Double Dep.</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left frontal</td>
<td>.81 + .042</td>
<td>.85 + .056</td>
<td>p &lt; .002</td>
</tr>
<tr>
<td>. min &amp; max:</td>
<td>.74 -- .81</td>
<td>.78 -- .967</td>
<td></td>
</tr>
<tr>
<td>Right frontal</td>
<td>.796 + .051</td>
<td>.836 + .062</td>
<td>p &lt; .02</td>
</tr>
<tr>
<td>. min &amp; max:</td>
<td>.7 -- .88</td>
<td>.73 -- .942</td>
<td></td>
</tr>
<tr>
<td>Left posterior</td>
<td>.842 + .048</td>
<td>.888 + .066</td>
<td>p &lt; .01</td>
</tr>
<tr>
<td>. min &amp; max:</td>
<td>.75 -- .94</td>
<td>.8 -- 1.04</td>
<td></td>
</tr>
<tr>
<td>Right posterior</td>
<td>.837 + .056</td>
<td>.893 + .079</td>
<td>p &lt; .01</td>
</tr>
<tr>
<td>. min &amp; max:</td>
<td>.74 -- .94</td>
<td>.8 -- 1.087</td>
<td></td>
</tr>
</tbody>
</table>
Cerebral Blood Flow in Dyshymnia

Figure 1: Mean & SD values of HMPAO uptake indexes; gender influence.

Four regions of interest were chosen according to literature data prior to 1991 and drawn conformed to Hoffman's rules (1979); luteo-external frontal and posterior parietal of both hemisphere. SPECT examination (Steindling, 1989) was performed as patients were lying down with eyes closed in a silent and darken room. Cerebral detection was achieved using a Tomomatic 64 (Medimatic Copenhagen) a highly sensitive system with rapid rotation allowing three tomographic planes to be viewed simultaneously with a 12 mm resolution. Uptake indexes were calculated by referring to both cerebellar hemisphere mean value. Single variable region by region variance analysis was used to calculate the effect of the diagnostic group on HMPAO fixation indices.

Our results (Table 2) indicated that major depressive patients CBF were lower in all the regions

67
tested than those with dysthymia (Figure 1, p. 67). The slight overlap of CBF values for the left frontal region, showed that this region may be particularly pertinent for differentiating between the two groups. Sex difference was significant solely in this region with a same effect within both groups characterised by lower CBF in women (Figure 2). No correlation was found between left frontal as well as other regions CBF and severity of the depressive symptomatology in either group. The unique correlative finding with clinical data was the significant correlation between length of the illness and low frontal CBF among dysthymics.

We were unable to define specific patterns for each group as we did not have control groups although the most marked differences between groups were noted in left frontal region. This region has been consistently quoted as an involved but not specific key region in affective disorders (Lhermitte, 1993) as well as in schizophrenia (Weimberger et al., 1986; Berman et al., 1993) or in long term cocaine abusers (Volkow et al., 1992) Recent dimensional analysis revealed that decrease
left frontal CBF was strongly associated with psychomotor retardation in major depression (Dolan et al., 1994) and psychomotor poverty in schizophrenia. The mean lower score of the dysthymic patients on the retardation scale provides an explanation of this difference.

These differences may be explained by the lower scores on retardation and depression scales in dysthymic patients thus suggesting a quantitative between group difference. If it was, we would have observed a correlation between CBF and rating scale scores, which we did not find. This lack of correlation suggests that the quantitative explanation is insufficient; therefore CBF measurements may be more sensitive to the inherent qualitative characteristics of the subgroups studied.

Laboratory and neurophysiological investigations which were performed on dysthymic patients disclosed some trait markers similar to the state markers of major depression (Howland and Thase, 1991; Akiskal, 1994). We reported in a previous study that patients of both groups gave results for a sensitive test of frontal dysfunctions which were significantly different compared with controls, the
Figure 4: A 54 year-old man experiencing a first episode double depression following 4 years of dysthymia. The day he was assessed, his score on MADRS was 35. SPECT image shows a right dominance asymmetry without significant left frontal decrease.

two groups being different both quantitatively and qualitatively; impairment within dysthymic patients was correlated with duration of the illness and not with the MADRS or retardation scale scores (Goudemand and Thomas, 1991). Specific frontal impairments appeared as important as those observed in major depression after a mean duration of the illness above 6 years (Thomas and Goudemand, 1992). This result was consistent with the correlation between length of the illness and low frontal CBF among dysthymic patients and may explain the partial overlap between the two groups especially within frontal areas.

There is a wide range of published conflicting results of clinical correlations with CBF or CMR in major depression when nearby two decades of literature are collected. One important reason of the controversies is provided by the methodological necessity to define regions of interest (ROI). The choice of ROI remains arbitrary and based upon anatomo-clinic references that do not take in account the connectivity of the living brain. Since physiopathology of affective disorders remains
unclear, this method may be insufficient or hazardous to observe specific functional changes in affective disorders.

Recent methods using statistical parametric mapping allow a pixel by pixel analysis of functional images and aim to map functional correlations by means of statistical quotients. The method of statistical parametric maps relies on drawing regions of interest in advance. Thus, Bench et al. (1993) using this method in a PET study on 40 patients experiencing major depression, described with the 15CO₂ inhalation technique: 1) a decrease CBF in the left dorsolateral pre-frontal cortex and left angular gyrus correlated with psychomotor slowing; 2) an increase CBF bilaterally in the posterior cingulate cortex and in the inferior parietal lobule correlated with anxiety and 3) an increase of left medial pre-frontal cortex correlated with cognitive impairment.

These data are consistent with the concept that key structures in the determinism of affective disorders (Cummings, 1993; Drevets, 1992). It suggests that CBF or CMR relate to symptomatic or dimensional modification as far as patients belong to the same nosographic type.

Moreover, some studies have examined patients with major affective disorders both in the illness phase and in the recovery state. PET studies (Baxter et al., 1989; Martinot et al., 1990; Bench et al., 1994) described a normalisation of left DLPFC CMR or CBF on recovery. SPECT studies are more conflicting; in on ongoing study we found as preliminary results with 20 patients significant change in lateralisation with a loss of right dominance on cortical regions and inverse results on subcortical regions. Initial high asymmetry gradient with right advantage in temporal regional CBF was significantly correlated with favourable outcome. These results indicate that repetitive brain imaging studies may be helpful in prognosis evaluation and treatment decisions.

SPECT sensitivity will probably remain behind PET that is sensitive to brain activity changes with low level of resolution. A limitation with PET is the cost, the technology, and the small size of patient samples. However PET gives important information on discrete changes of localised structures, and provides with radiopharmaceutical compounds imaging of brain receptors that are of interest in mood disorders. This represents a unique opportunity to assess the neurotransmitters hypothesis of mood disorders.

Receptor studies have been conducted on very small samples with different treatment challenges. Sleep deprivation in affective disorders focusing on dopamine with D2 receptor blockade (Ebert et al., 1994) and in primary (D’haenen et al., 1992) or secondary (Mayberg et al., 1995) depression with two serotonin S2 receptor radioligand 11C spiperon with PET and 1123 ketanserin with SPECT, reporting consistent results with the biological hypothesis.

PET findings may therefore be of interest to guide SPECT studies that would replicate and test CBF or receptor binding results to a wider range of patients. SPECT may assist practitioners in assessing patients by making measures of biological functions that are not otherwise accessible. SPECT is certainly not a diagnostic tool, at the very most it can be clinically helpful for distinguishing primary depression from Alzheimer’s disease in elderly patients with mood disorders (Golan et al., 1996). SPECT may rather be able to guide therapy of patients with unfavourable outcome that are over represented in dysthymia by imaging impairment of brain functional organisation as therapeutic management progresses: this could be conceivable with a solid knowledge about brain imaging. Unfortunately, advance in the area of dysthymia is hampered by the lack of data, with, to our knowledge, a total of only 4 brain imaging studies mentioning dysthymia or related disorders.

Our results support the idea that dysthymic patients experiencing double depression share some
brain functional aspects with major depressed patients. Differences, especially in left frontal areas, may be partially explained by psychomotor retardation that was the main episode’s clinical distinction between groups. However the lack of correlations with clinical severity may also reflect a between group qualitative distinction based on mixed state and trait markers within dysthymic patients.

Further studies on dysthymia with SPECT should focus on successive brain imaging examinations to observe the effects of remission or worsening of symptoms. Cognitive therapy pharmacological treatment or a combination of both should be associated with (Mann et al., 1996; Fisher et al., 1995) PET studies. Both type of studies could provide information about trait dependant abnormalities in dysthymia co-occurring with other conditions (Akiskal et al., 1994; Arriaga et al., 1995), and about the mixed trait and state dependant abnormalities in double depression could also help to determine predictive brain imaging patterns of treatment response.

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DYSTHYMIA IN PATIENTS WITH STROKE AND NEUROLOGICAL DISORDERS

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INTRODUCTION

If one considers the types of depressive disorder that may occur in patients with stroke, it is not immediately obvious that dysthymic disorder is one of them. The major problem in the applicability of this diagnostic category to patients with stroke is the duration of symptoms. Dysthymic disorder requires that the syndromic cluster of depressive symptoms be present most of the time for more than 2 years. This long duration suggests that these disorders may be related to characterological vulnerabilities or interpersonal or environmental stressors over many years and does not involve the same neurophysiological brain abnormalities as major depression. In addition, stroke usually has a sudden cataclysmic onset. Thus, waiting for 2 years to diagnose a post-stroke dysthymic disorder or being sure that the dysthymic disorder began after the onset of stroke does not seem to be very clinically useful.

In order to deal with this duration of symptom problem and to determine whether there is a less severe form of depression associated with neurological disease, I and other authors (Eastwood et al., 1989; Burvill et al., 1995) have used the Research Diagnostic Criteria (RDC) term "minor depression" to refer to these depressions. Most of our studies, however, have used the symptom (but not duration) criteria for dysthymic disorder.

Many psychological and social symptoms used by DSM-III-r criteria for dysthymia defined a group of patients which were just as numerous as major depression. Other authors such as House et al. (House et al., 1991) have used the term dysthymia to refer to patients who developed depression 2 or more years prior to a stroke and remained depressed after the stroke. These patients met the duration as well as symptom criteria for dysthymic disorder but could not be considered to have dysthymia related to stroke. Eastwood et al. (1989) and Morris et al. (1990) used the RDC criteria for minor depression which was a subsyndromal disorder of major depression requiring at least 2 but less than 5 major depressive symptoms. Recently, DSM-IV has introduced the category of minor depression to the official diagnostic manual as a research category. This diagnosis is based on the existence of depressed mood or loss of interest and 1 to 3 additional symptoms of major depression (ala RDC definition).
Dysthymia in Patients with Stroke and Neurological Disorders

Ultimately, no matter how dysthymia or minor depression is defined, the disorder must be validated as an entity distinct from major depression. Throughout many of the studies of neuropsychiatric disorders that we have conducted, we have looked for findings that would, or would not, support the distinction of dysthymic or minor depression as a separate form of depression associated with neurological disease. In this paper, I will review these findings as well as findings by other investigators which address this important issue of whether stroke is associated with a less severe form of depression than major depression. These studies must determine whether post-stroke dysthyemic depression (used interchangeably with the term minor depression) has its own symptoms, course, mechanism, etiology, and response to treatment.

PREVALENCE

The prevalence of depression in stroke patients was examined among patients admitted to an acute stroke unit, a general hospital ward, a rehabilitation center, and in patients living in the community. A summary of the findings from studies that used standardized criteria for the diagnosis of dysthymic (or minor) depression are shown on Table 1. Among patients admitted to a stroke unit within the first 4 weeks after a stroke lesion, we found a prevalence of dysthymia of 18% (Castillo et al., 1993). In a population-based study that included a consecutive series of 294 stroke patients examined 4 months after the acute event, Burvill et al. (1995) reported a prevalence of minor depression of 8%. Finally, Morris et al. (1990) reported a prevalence of dysthymia of 22% among 94 patients admitted to a rehabilitation unit.

One important issue to be addressed is the longitudinal evolution of post-stroke dysthymia. In a 2-year longitudinal study of 103 acute stroke patients, we found that among patients with an inhospital diagnosis of dysthymia, 57% were depressed at the 1-year follow-up and 75% were depressed at the 2 year follow-up (Robinson et al., 1987).

This suggests a prolonged duration of depression for these patients with periods of major depression intermixed with dysthymic disorder. Other authors (Morris et al., 1990; House et al., 1991) reported a shorter duration of post-stroke dysthymia, and this discrepancy may result from differences in case ascertainment (i.e., community-dwelling patients or patients admitted to a rehabilitation center in House’s et al. and Morris’ et al. studies respectively, as compared to acute stroke patients in our study) or from variability in the etiology of minor depression with some cases being true dysthyemic disorder and long duration depressions while others are more akin to adjustment disorders with duration of less than 6 months.

In conclusion, dysthymia is a frequent finding in patients with acute stroke lesions, and, in some patients, may last for more than 2 years if left untreated.

CLINICAL CORRELATES OF POST-STROKE DYSTHYMIA

In a recent study, Morris et al. (1991) found significantly more severe impairments in activities of daily living (ADLs) in stroke patients with dysthymia as compared to non-depressed stroke patients. On the other hand, no differences in ADLs were found between major depressed and
Table 1: Prevalence of Dysthymia in Studies of Patients with Stroke

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Patient Population</th>
<th>Nr.</th>
<th>Criteria</th>
<th>Dysthymia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robinson, '93</td>
<td>Acute Hospital</td>
<td>309</td>
<td>DSM-III-r</td>
<td>18</td>
</tr>
<tr>
<td>Eastwood, '89</td>
<td>Rehab Hospital</td>
<td>87</td>
<td>SADS-RD</td>
<td>40</td>
</tr>
<tr>
<td>Morris, '90</td>
<td>Rehab Hospital</td>
<td>99</td>
<td>CIDI-D-II</td>
<td>21</td>
</tr>
<tr>
<td>Shubert, '92</td>
<td>Rehab Hospital</td>
<td>18</td>
<td>DSM-III-r</td>
<td>44</td>
</tr>
<tr>
<td>House, '91</td>
<td>Community</td>
<td>89</td>
<td>PSE-D-III</td>
<td>12</td>
</tr>
<tr>
<td>Herrmann, '93</td>
<td>Acute Hospital</td>
<td>21</td>
<td>RDC</td>
<td>14</td>
</tr>
<tr>
<td>Burvill, '95</td>
<td>Community</td>
<td>294</td>
<td>PAS-D-III</td>
<td>8</td>
</tr>
</tbody>
</table>

Nondepressed stroke patients. Morris et al. (1991) reported a significant inverse correlation between Barthel ADLs scores and depression scores among dysthymic patients, demonstrating that greater disability was associated with more severe depression. Based on these findings (Morris et al., 1991), speculated that dysthymia may be a psychological reaction to the functional disabilities produced by stroke. Several studies have examined the presence of cognitive impairments in patients with post-stroke dysthymia. Using the Mini-Mental State Exam, we could not find differences between dysthymic and non-depressed stroke patients (Robinson et al., 1986), and similarly negative results were found with a more comprehensive neuropsychological battery (Bolla-Wilson et al., 1989). On the other hand, patients with major depression showed significantly more severe cognitive impairments than patients without depression, demonstrating important differences in the correlates (and perhaps mechanism) of major depression and dysthymia following stroke. In contrast, however, impaired physical recovery from stroke associated with depression (Parikh et al., 1990) and increased mortality associated with depression (Morris et al., 1993) did not find differences between the effects of major depression and dysthymia.

We have consistently reported a significant association between major depression and left hemisphere anterior lesions involving cortical (mostly frontal) and subcortical (mainly the basal ganglia) areas (Starkstein et al., 1987). These findings have been independently replicated by some but not all authors (Astrom et al., 1993; Herrmann et al., 1993; House et al., 1990). Furthermore, we have reported that the severity of depression was significantly correlated with the proximity of the lesion to the frontal pole (Robinson et al., 1984). On the other hand, we have recently found that dysthymia in the acute post-stroke period was significantly correlated with proximity of the lesion to the occipital pole (Figure 1) (unpublished data). These findings suggest that, during the acute stroke period, major and dysthymic depressions are associated with different lesion locations.

**TREATMENT OF POST-STROKE DYSTHYMIA**

Few studies have examined the usefulness of antidepressant drugs in the treatment of post-stroke depression using a randomized, double-blind, and placebo-controlled design, but none of
Dysthymia in Patients with Stroke and Neurological Disorders

Figure 1. Severity of depression using the Hamilton Depression Scale was significantly correlated with the distance of the lesion's posterior border from the frontal pole. In contrast to major depression, dysthymia was more severe with more posterior lesions (this included both right and left hemisphere lesions).

them separated stroke patients into groups with major depression or dysthymia. We demonstrated the efficacy of the tricyclic antidepressant nortriptyline (up to 100 mg/d) in the treatment of post-stroke depression (Lipsey et al., 1984), and recently Andersen (1995) showed the usefulness of the selective serotonin reuptake inhibitor citalopram. Future studies should examine whether post-stroke major depression or dysthymia show a differential response to treatment with antidepressant drugs.

CONCLUSIONS

Uncertainties about the duration of the depressive disorder following stroke and evidence that dysthymic depression frequently has a duration of less than one year has made the 2-year duration criteria for dysthymia untenable in the stroke patient populations. Evidence has been found, however, that there are a group of post-stroke depressed patients who do not meet the criteria for major depression. These subsyndromal depressive disorders have also been called minor depression and have been differentiated from major depression.

Following stroke, dysthymia has a more variable duration than major depression with some depressions lasting for more than 2 years. Furthermore, dysthymic depression was found to increase in severity with more posterior (occipital) hemispheric stroke lesions while major depression increased in severity with more anterior lesions. Major depression but not dysthymia was associated with cognitive impairment. In contrast, however, both major and dysthymic depression are associated with increased mortality following stroke. All of these studies have provided evidence that supports the validity of dysthymia as a distinct etiologically different form of depression in patients with stroke.

Further studies should examine differences in treatment response between major depression and dysthymic depression. Psychological and social treatments may play a greater role in the care of patients with dysthymia than major depression but the long term physical and cognitive as well as emotional outcome will be an important measure of treatment success in patients with comorbid dysthymia and stroke.
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DYSTHYMIA IN PARKINSON'S DISEASE

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PREVALENCE

Few studies have examined the prevalence of dysthymia in Parkinson's disease (PD) using a structured psychiatric interview. We used the Present State Exam (PSE) to assess the frequency of depression among PD patients examined in a general neurology clinic at the time of their regular follow-up visits (Starkstein et al., 1990). We found a prevalence of depression of 41% (half of the patients having dysthymia and the other half major depression), and 20% of the patients who were not depressed at the time of the psychiatric evaluation had a positive history of depression. Gotham et al. (1986) also used the PSE to examine the prevalence of depression in 40 patients with PD, and reported a high frequency of simple depression, tension, irritability, worrying, and loss of interest and concentration.
THE COURSE OF DEPRESSION IN PARKINSON'S DISEASE

One relevant question is when during the evolution of PD is depression most prevalent. In a cross-sectional study we found that 29% of 21 patients with major depression were depressed before the onset of motor symptoms, whereas only 5% of patients with dysthymia and 2% of those without depression had a prior history of depression (Starkstein et al., 1990). These findings demonstrate that most dysthymias start after the onset of PD, and suggest that dysthymia may be an emotional reaction to the incipient motor deficits of PD.

In a 1-year follow-up study of this same sample of PD patients, we found that 26% of the patients with an initial diagnosis of dysthymia still had dysthymia at the 1-year follow-up, while 11% had major depression, and 63% had no depression (Starkstein et al., 1992). On the other hand, 56% of patients with major depression at the initial evaluation still had a major depression at follow-up, 33% had dysthymia, and 11% were not depressed ($X^2=11.5$, df=1, p<.001). Thus, while most major depressions in PD may last for more than 1 year, dysthymia in PD has a significantly shorter duration.

CORRELATES OF DEPRESSION IN PD

Several studies have examined the presence of a significant association between depression and deficits in ADLs in PD. While some of them reported a significant correlation between depression and deficits in ADLs (Gotham et al., 1986), we found this association to be strongest in the late stages of the illness (Starkstein et al., 1990). In our follow-up study we demonstrated that major depression but not dysthymia was significantly associated with a greater decline in ADLs as compared to non-depressed PD patients (Starkstein et al., 1992). Furthermore, major depressed patients showed a significantly faster progression along the stages of the illness, and a significantly faster cognitive decline than both dysthymic and non-depressed PD patients. Taken together, these findings demonstrate that major depression predicts a more aggressive course of PD as compared to dysthymia, and suggest that major depression and dysthymia in PD may have a different mechanism.

MECHANISM OF DYSTHYMIA IN PD

Both psychological and biological factors were proposed to explain the presence of depression in PD. Major depression in PD may be related to biological factors, since a high proportion of these patients start with depression before the onset of motor symptoms. Moreover, major depression in PD is weakly associated with deficits in ADLs, but is significantly associated with both deficits on frontal lobe-related cognitive tasks (Starkstein et al., 1989) and significant metabolic deficits in the inferior frontal lobes (Mayberg et al., 1990).

On the other hand, dysthymia in PD usually starts after the onset of PD, is not associated with significant cognitive impairments, and does not predict further declines in cognitive and physical functions (Starkstein et al., 1992). Thus, dysthymia in PD may represent an emotional
Dysthymia in Parkinson’s Disease

reaction of predisposed individuals when confronted with the...physical limitations of the disease.

TREATMENT OF DEPRESSION IN PD

There are few controlled studies on the efficacy of antidepressants in PD. While tricyclic drugs such as imipramine, desipramine, and nortriptyline were associated with significant mood improvements (Klaasen et al., 1995), whether these drugs have a differential effect upon major depression or dysthymia has not been empirically examined. Other antidepressants such as the selective serotonin reuptake blockers were reported to be effective in uncontrolled case series (Klaasen et al., 1995). Cognitive therapy may also be a useful treatment modality, but whether dysthymia in PD is amenable to this kind of treatment should be demonstrated in future controlled studies.

ACKNOWLEDGMENTS

This study was supported in part by grants from the Raúl Carrea Institute of Neurological Research-FLENI, the CONICET, and the Fundacion Perez Companc. The author thanks Dr. Robert Robinson, Thomas R. Price, John R. Lipsey, Rajesh Parikh, J. Paul Fedoroff, Ricardo Jorge, Helen Mayberg and Phillip Morris who participated in many of the studies described.

REFERENCES


85
DYSTHYMIA IN ALZHEIMER’S DISEASE

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PREVALENCE

The prevalence of depression in AD has been reported to range from 10% to more than 80% (Wragg and Jeste, 1989). This wide variability may be related to important methodological differences between studies, such as the assessment of AD patients referred to either a psychiatric clinic, an AD clinic, or living in a community, the use of “ad-hoc” diagnostic criteria for depression, and the exclusion of AD patients with a prior history of depression.

In a recent cross-sectional study, Migliorelli et al. (1995) examined the prevalence of depression in a consecutive series of 103 patients attending an AD clinic. Using a structured psychiatric interview (the Structured Clinical Interview for DSM-III-R), they found that 28% of the patients had dysthymia and 23% had major depression.

CORRELATES OF DEPRESSION IN AD

One important question is whether dysthymia and major depression start at different periods during the cognitive decline. Migliorelli et al. (1995) found that while most patients with dysthymia were in the stage of mild dementia, the prevalence of major depression was similar along the stages of mild, moderate, and severe dementia. Moreover, while half of the patients with major depression had the onset of depression before the onset of dementia, 86% of the dysthymic patients had the onset of depression after the onset of dementia.
Davous et al. (1995) examined the longitudinal evolution of depression in a cohort of 124 patients with dementia. At the initial evaluation, the prevalence of dysthymia and major depression was 23% and 23%, respectively. Thirty-three percent of this group was still depressed at the 3-month follow-up, while 11% were depressed at the 6-month follow-up. Starkstein et al. (in preparation) examined the prevalence of depression in 47 AD patients followed for 1-2 years. At the initial evaluation 19% of the patients had major depression, 34% had dysthymia, and 47% were not depressed. After a mean follow-up of 16 months, 58% of the patients with major depression at the initial evaluation were still depressed, whereas only 28% of patients with dysthymia at the initial evaluation, and 21% of the non-depressed patients at the initial evaluation were depressed at follow-up. During the follow-up period, all 3 groups showed similar declines in cognitive status and activities of daily living.

Starkstein et al. (1995) have recently examined the rCBF correlates of dysthymia and major depression in AD using 99mTc-hexamethyl-propylene-amine oxime (HMPAO) and single photon emission tomography (SPECT). They reported that AD patients with major depression had significantly lower left temporo-parietal perfusion as compared to non-depressed AD patients. On the other hand, AD patients with dysthymia had a significantly better global rCBF than AD patients with either major or no depression which may reflect the mild stage of dementia found in the majority of patients with dysthymia and AD.

MECHANISM OF DEPRESSION IN AD

Several findings suggest that major depression in AD may be related to biological factors. Half of the AD patients with major depression starts with depression before the onset of cognitive decline, major depression in AD lasts significantly longer than dysthymia, and has a similar prevalence along the stages of the illness.

Moreover, major depression in AD is significantly associated with both left temporo-parietal hypoperfusion and significantly higher theta relative power in posterior brain areas of both hemispheres as compared to non-depressed AD patients (Pozzi et al., 1993). Finally, several authors reported a significant association between major depression in AD and neuronal depletion in the locus coeruleus and the raphe nuclei as compared to non-depressed AD patients (Zubenko and Moosy, 1988).

On the other hand, dysthymia in AD usually develops after the onset of the cognitive decline, has its highest prevalence in the early stages of the illness, and has a significantly shorter longitudinal evolution than major depression. Moreover, dysthymic AD patients do not show significant qEEG differences as compared to non-depressed AD patients, and have a significantly better CBF than both major depressed and non-depressed AD patients. Finally, dysthymic AD patients show a significantly better awareness about their cognitive impairments than AD patients with either major or no depression, and as the severity of unawareness increases the prevalence of dysthymia decreases (Migliorelli et al., 1995). Taken together, the above findings suggest two types of depression in AD: major depression produced by disruption of biological mechanisms, and dysthymia produced by an emotional reaction of predisposed individuals when confronted with their cognitive impairments.
TREATMENT OF DEPRESSION IN AD

Few studies have examined the usefulness of antidepressant drugs in patients with AD using controlled designs. Reifler et al. (1989) demonstrated that both imipramine and placebo produced significant mood improvements in depressed AD patients, but imipramine was not better than placebo. In a recent randomized, double-blind, placebo-controlled study Petracca et al. (1996) found a significantly better antidepressant effect for clomipramine as compared to placebo, although the latter also produced a significant antidepressant effect. However none of these studies separated patients into major-depressed and dysthymic groups, and this issue should be examined in future studies.

ACKNOWLEDGMENTS

This study was supported in part by grants from the Raúl Carrea Institute of Neurological Research-FLENI, the CONICET, and the Fundacion Perez Companc. The author thanks Dr. Robert Robinson, Thomas R. Price, John R. Lipsey, Rajesh Parikh, J. Paul Fedoroff, Ricardo Jorge, Helen Mayberg and Phillip Morris who participated in many of the studies described.

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DYSTHYMIA IN MULTIPLE SCLEROSIS

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INTRODUCTION

Multiple Sclerosis (MS), a chronic disabling disease of the central nervous system (CNS), produces with its relapsing-remitting and/or chronic-progressive course marked changes in the personal, emotional, affective, and interrelational life of the patient. The process of becoming aware of one's own limitations is associated with increasing dependence and isolation. Loss, mourning, and feelings of death or suicide are not uncommon. A perception of loss brings about symptoms of anxiety, dysthymia and depression. Here we review some of the literature on depression in MS and present our own data on dysthymia in MS.

* Consultant
** Assistant, Psychiatric Service
DEPRESSION IN MS

The description of psychological disorders associated to MS had already been pointed out by Charcot in 1899 and Vulpian in 1896, as well as by Ombredane in 1929. Cottrell and Wilson (1926) stated that affective disorder is the most important clinical symptom in MS, and that no single neurological symptom is more frequent than depression in these patients. In the literature, we can find considerable data on the high impact of depression in MS. Nevertheless, different studies differ in regard to the evaluation of depression, and to its relevance. The reported rates of depression in MS vary from 14% to 57% (Joffe et al., 1987; Minden et al., 1987; Schiffer et al. 1988; Surridge, 1969; Whitlock and Siskind, 1980). The percentage of major depression evaluated for the time preceding the neurological disease does not differ significantly from that of the general population aged between 25 and 45 (Minden, 1991), whereas the incidence of major depression is significantly higher after the onset of MS compared with other neurological or medical pathologies and with the general population (54-60%) (Minden, 1991).

Within mood disorders, bipolar disorder seems to be, according to several authors (cited above), frequently represented, as there is a considerable rate of mania and hypomania in MS. The reason for the high frequency of bipolar disorders in MS patients remains unclear because such disorders could be precipitated not only by MS itself, but also by corticosteroid therapy. Interestingly, reports on the rates of euphoria have changed over the course of this century: euphoria in MS was considered very frequent in the first works, up to 63% by Cottrell and Wilson (1926), but lately it has been reported in much lower frequency (Cazzullo et al., 1989).

In general, depression reveals itself clinically as moderate and severe: patients are often irritable, reactive, not interested and discouraged (Joffe et al., 1987, Minden and Schiffer, 1993). Depression symptomatology in MS does not seem, according to some authors (Minden et al., 1991), directly connected to impaired cognitive functioning, whereas for other authors (Schiffer and Caine, 1991), mild to moderate cognitive impairment secondary to depression is common in MS, and may be more impairing than physical symptoms for some patients (Beatty, 1993).

A recent study pointed out that depression is associated to social stress, but not to the degree of neurological impairment, disability, or handicap. It is suggested that depression, especially in relapsing-remitting MS, may arise when the patient becomes aware of his or her impairment in occupational performance and in close personal relationships (Gilchrist and Creed, 1994).

Some studies report the presence of a correlation between the severity of depression and the seriousness of MS, however such correlation is not emphasized in other works (Whitlock and Siskind, 1980; McIvor et al., 1984; Rabins et al., 1986; Joffe et al., 1987).

Starting in 1983, our group contributed to propose a biological definition of mood disorders in MS as an expression of a common immunogenetic structure between the two pathologies (Cazzullo et al., 1983). In that context, it was found that patients, as well as in their first degree relatives, had identical HLA haplotypes with a 55% frequency.

Several authors (Goodstein and Ferrel, 1987; Whitlock and Siskind, 1982; Joffe et al., 1987; Barrios and Quemada, 1990; Minden and Schiffer, 1991) assert that depression in MS patients can occur before, during or after the acute neurological episode.

Barrios and Quemada (1990) have proposed three hypotheses about the nature of depression in MS:

1. A first hypothesis states the coincidence between the two pathologies.
Table 1: Clinical Characteristic of MS Sample

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr. of patients</td>
<td>258</td>
</tr>
<tr>
<td>Age, years (range)</td>
<td>20-40</td>
</tr>
<tr>
<td>Sex (males/females)</td>
<td>102-156</td>
</tr>
<tr>
<td>Education, years (range)</td>
<td>8-18</td>
</tr>
<tr>
<td>Duration of illness, years (range)</td>
<td>2-5</td>
</tr>
</tbody>
</table>

2. A second hypothesis suggests the reactive nature of depression (reaction to fear or loss of health that, according to the authors, can be caused by any severe illness).

3. The third hypothesis is based on organic factors: the depressive pathology is considered the result of neurobiological changes that are the same as or in any case parallel to those causing the neurological symptoms.

 Such a model, based on genetic, biochemical, immunological and/or anatomical mechanisms (presence of demyelination plaques in specific cerebral areas, e.g. limbic system) might help explain the onset of depression both before and after the onset MS.

SUICIDE

Because of the high incidence of the "depressive" phenomenon in MS patients, some authors assessed the presence of suicide, suicide attempts and suicide thoughts in the history of these patients. Kahana et al. (1971) observed 3% of suicides in a sample of 295 patients. Whitlock and Siskind (1980) out of 30 patients reported 1 suicide, 1 attempted and 13 plans of suicide. Minden and Schiffer (1991) out of 50 patients identified moderate suicide ideation in 5 subjects and 10 suicide attempts in 6 patients. Since beta-interferon started to be used in the treatment of MS, 2 suicides and 4 attempted suicides were observed.

RESEARCH STUDY: DYSTHYMIA IN MS

Our study was focused on dysthymia in MS patients hospitalized in the "University M.S. Center" of the Pro Juventute Don C. Gnocchi Foundation in Milano. The total number of first admissions in our center, for the years 1988-1990, was 1017. Psychiatric consultation was requested by 258 patients (25.3%). Consultation was requested according to the clinical judgment of the neurologist in the light of the quality, quantity and the severity of psychiatric symptomatology. This protocol may have led to underestimation of the rates of psychiatric morbidity, because often initial, mild psychiatric symptoms in MS patients may not be perceived by the attending neurologist, and could therefore be undetected (Sullivan et al., 1995). Table 1 reports the clinical characteristics of our sample.

Each patient was evaluated by means of a psychiatric assessment and examination, and mental test battery composed by BPRS, Hamilton Anxiety and Depression Scales, Beck Depression Invent-
tory, STAI Test for anxiety. Furthermore, each patient received the WAIS test and a neuropsychological battery, in order to evaluate cognitive functioning.

Table 2 summarizes the various psychiatric disorders (according to DSM-III-r) observed in our sample of MS patients. Mood disorders, on the whole, are represented by 68 patients (26.4% of the total sample).

Table 3 describes the incidence rate of the different mood disorders. Dysthymia presents a remarkable incidence (10.5%), the highest within the whole group of mood disorders.

Our sample has subjects of different educational levels. No specific age prevalence peak was observed; subjects had had a diagnosis of MS for 2 to 5 years.

Dysthymia was not correlated to the degree of motor or cognitive disability and showed an increase with the increase of the duration of illness.

Almost half of the patients were partially socially impaired, and working ability was almost totally impaired in the whole sample. Because in general MS patients leave their jobs very early, patients with dysthymia showed no difference in work impairment compared to the others.

Mood disorders showed a remarkable prevalence in first-degree relatives (26.5%), and dysthymia was the most common diagnosis (15%).

Table 2: DSM-III-r Diagnoses in MS patients. Number of patients = 258

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>%</th>
<th>Nr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personality Disorder</td>
<td>31.0</td>
<td>80</td>
</tr>
<tr>
<td>Mood Disorder</td>
<td>26.4</td>
<td>68</td>
</tr>
<tr>
<td>Adjustment Disorder</td>
<td>19.4</td>
<td>50</td>
</tr>
<tr>
<td>Organic Mental Disorder</td>
<td>12.4</td>
<td>32</td>
</tr>
<tr>
<td>Any Psychiatric Disorder</td>
<td>10.9</td>
<td>28</td>
</tr>
</tbody>
</table>

Table 3: Mood Disorder in MS Patients. Total % of patients with mood disorder = 26.4

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th></th>
<th>Males</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nr. 156</td>
<td>Nr.</td>
<td>Nr. 102</td>
<td>Nr.</td>
<td>Nr. 258</td>
<td>Nr.</td>
</tr>
<tr>
<td>Depression Disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysthymia</td>
<td>11.5</td>
<td>18</td>
<td>8.8</td>
<td>9</td>
<td>10.5</td>
<td>27</td>
</tr>
<tr>
<td>Major depression</td>
<td>4.5</td>
<td>7</td>
<td>3.9</td>
<td>4</td>
<td>4.3</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Females</th>
<th></th>
<th>Males</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nr. 156</td>
<td>Nr.</td>
<td>Nr. 102</td>
<td>Nr.</td>
<td>Nr. 258</td>
<td>Nr.</td>
</tr>
<tr>
<td>Depression Disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressed bipolar</td>
<td>1.3</td>
<td>2</td>
<td>1.0</td>
<td>1</td>
<td>1.2</td>
<td>3</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar Disorder, manic</td>
<td>1.9</td>
<td>3</td>
<td>2.9</td>
<td>3</td>
<td>2.4</td>
<td>6</td>
</tr>
<tr>
<td>Bipolar Disorder, not elsewhere classified</td>
<td>7.0</td>
<td>11</td>
<td>9.8</td>
<td>10</td>
<td>8.2</td>
<td>21</td>
</tr>
</tbody>
</table>
Dysthymia in Multiple Sclerosis

We found an important relationship between the onset of mood disorders and the onset of MS. In our sample, cases were divided into groups according to whether depression appeared before, concomitant with, or after the onset of MS. We found that the majority of mood features arising after the diagnosis of MS have been ascribed to dysthymia, whereas those appeared concomitantly or before MS diagnosis consisted of major depression.

We did not find any manic features arising before the neurological diagnosis, whereas hypomanic signs have been noticed before and after the MS neurological diagnosis.

Suicide, Attempted Suicide, Suicidal Plans

Our material offered us the opportunity to observe that, among 68 MS patients with mood disorders, 28 (41.2%) showed suicidal thoughts, revealed by the psychiatric interview as well as by mental tests. If we accurately examine the responses to the HDS, we can observe that the majority of patients believe that life becomes very difficult to be accepted. However, an analysis of Beck Depression Inventory results shows that the majority of patients are ambivalent toward suicide, which they consider more as a fantasy than a realistic event.

Table 4 shows that we did not record any case of suicide during the course of the disease in our sample, whereas most of attempted suicides (7) were performed after MS diagnosis had been explicitly given to the patient (10.3%).

If we pay attention to the behavioral modalities, as well as to the repetition of the gesture, we can detect in most cases the utilization of gas and antidepressant drugs, representing a serious attempt, or multiple attempted suicides. In our sample, none of the patients with dysthymia had suicide thoughts. All attempted suicides were performed by patients affected by major depression.

**DISCUSSION**

In our sample, dysthymia only occurred after the MS diagnosis had become evident and known to the patient. Symptoms of dysthymia may be neglected because the verbalization of the patient is scarce or incomplete, especially in the doctor-patient relationship with the neurologist.

**Table 4:** Suicide - Attempted suicide - Suicidal thoughts

<table>
<thead>
<tr>
<th></th>
<th>Nr.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicidal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attempted Suicide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before MS Diagnosis</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>After MS Diagnosis</td>
<td>7</td>
<td>10.3</td>
</tr>
<tr>
<td>In Dysthymic Patients</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Suicidal Thoughts</td>
<td>28</td>
<td>41.2</td>
</tr>
</tbody>
</table>
Table 5: Synthesis

<table>
<thead>
<tr>
<th>Mood Disorders</th>
<th>Dysthymia</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood disorders may be an initial symptom of MS, with such features like fatigue, uneasiness, dysphoria</td>
<td>Dysthymia is markedly present among mood disorders in MS patients</td>
<td>A combined treatment of psychopharmacology plus therapy is recommended</td>
</tr>
</tbody>
</table>

The main source of information was the clinical history obtained from the patient and from relatives. The analysis the patients' histories made it possible to collect data on the use of psychotropic drugs (anxiolytics and antidepressants) prior to the onset of MS.

Although gender plays a role in mood disorders we did not report a clear difference between sexes. On the whole group of 258 patients with mood disorders we registered 26.3% of females and 26.5% males. Furthermore no statistically significant differences have been found regarding sex among major depression and bipolar disorder. In dysthymia, a slightly higher prevalence of females (11.5% vs. 8.8% in males) was observed. The age group of our sample was mostly young with few years of disease.

It should be noted that the incidence of depression and dysthymia and MS are usually located in the same range of age.

A possible relationship may occur between dysthymia and dependent personality disorder, marked by an excessive need to be taken care of that leads to submissive and clinging behavior and fears of separation.

The role of the family had been assessed by studies of expressed emotion (EE) that showed low values of EE before the diagnosis, and a subsequent moderate increase after the diagnosis had been communicated by the neurologist.

In our study, the cognitive disturbances were absent or mild (slight impairment in attention), and the type of clinical course (relapsing-remitting vs. chronic progressive) was not found to consistently influence the presentation of affective or cognitive samples, similarly to what has been described by Moller et al. (1994).

Corticosteroid treatment was related to the presentation of depression and mania in patients with features of major depression or bipolar disorder.

In our experience, combined treatment, consisting of psychopharmacology and psychotherapy, has provided satisfactory results.

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Dysthymia in Multiple Sclerosis


DYSTHYMIA IN EPILEPSY

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INTRODUCTION

In its Greek origins, the term "dysthymia" means "ill-humoured" and can be traced back to the description of the melancholic temperament by Hippocrates (The WPA Dysphoria Working Group [WPA], 1994). It is therefore of interest that the first description of a mood (depressive) disorder and epilepsy was also attributed to Hippocrates when he commented: "melancholics ordinarily become epileptics and epileptics melancholics; of these two states, what determines the preference is the direction the malady takes: if it bears upon the body, epilepsy; if upon the intelligence, melancholy" (Lewis, 1934).
DYSTHYMIA

Before examining the concept of dysthymia (DYS) in people with epilepsy (PWE), it may be worth reminding ourselves of some ideas about the concept DYS. DYS is a concept introduced in DSM-III (American Psychiatric Association, 1980) and is chronic depression of mood (exceeding 2 years) which does not currently fulfill the criteria for recurrent depressive disorder (RDD), mild or moderate severity, in terms of either severity or duration of the individual episodes, although the criteria for mild depressive episode may have been fulfilled in the past, particularly at the onset of the disorder (World Health Organisation [WHO], 1992). DYS usually begins in early adult life and lasts for at least several years, sometimes indefinitely. It replaces and subsumes depressive neurosis, depressive personality disorder, neurotic depression, (with more than two years duration), neurasthenia, persistent anxiety depression and other mild chronic depressions (WHO, 1992; Hirschfield, 1994).

Of importance is that many experts consider that large areas of overlap exist between the definitions of DYS, major depressive disorder (MDD) and personality disorder (Hirschfield, 1994; WPA, 1994). It seems that in the past, at least some individuals with the diagnosis of “neurotic depression” may have had DYS: thus, Akiskal et al. (1978) documented a prospective follow-up of neurotic depressives; 40% were diagnosed as having a MDD, while many of the remainder were thought to have DYS. In an epidemiological catchment area (ECA) study, 75% of people with DYS had other disorders such as MDD and anxiety. Despite being included in both ICD 10 (WHO, 1992) and DSM IV (American Psychiatric Association [APA], 1994), questions are still raised about the validity of the diagnosis of DYS: can DYS be better conceptualised as a personality (or neurotic character) disorder (WPA, 1994) and, secondly, in particular can DYS really be distinguished from MDD (Hirschfield, 1994; WPA, 1994)? Of note is that if an individual has DYS with superimposed MDD, they are said to have “double depression” (Keller et al., 1983). It does seem, however, that particularly characteristic symptoms of DYS include anger, irritability and anxiety; moreover, the symptoms consistently used to define MDD and DYS respectively differ in severity and duration, rather than in kind (WPA, 1994).

As the studies referred to in this presentation span the years, if DSM (American Psychiatric Association) criteria have been fulfilled, DSM will simply be mentioned, and not DSM-III, DSM-III-r, DSM-IV etc.

DYSTHYMIA IN PWE

There have been few documentations of DYS in the context of PWE, although much has been written about depression in PWE. Firstly, let us examine the studies which have particularly mentioned DYS in PWE. Mendez et al. (1986) conducted a two part investigation. In the first, they mailed a questionnaire to 503 PWE of whom 175 (35%) responded. They were compared with 70 (38%) of 186 matched controls; 55% of the index (PWE) group reported depression, compared with 30% of controls. In the second part, Mendez et al. (1986) identified all PWE in-patients in a psychiatric hospital, and compared 20 depressed PWE with 20 depressed non-epileptics; all patients met DSM criteria for MDD. The 20 depressed PWE were characterised by significantly more
"endogenous" rather than "neurotic" traits or features, with a more abnormal affect, more psychotic phenomena (hallucinations and delusions), paranoia, irritability, humourlessness and a greater background of underlying chronic DYS (p < .001). The response to medication was noted to be inconsistent.

The only other study to comment on DYS was that of Thompson et al. (1992) who investigated 27 patients with psychogenic seizures (PS) and compared them to 22 PWE using the Millon Clinical Multiaxial Inventory (MCMI), a short, easy to administer version of the Minnesota Multiphasic Personality Inventory. Results showed that patients with PS scored significantly higher on MCMI scales Axis I of Anxiety, Somatoform and DYS, as well as the Axis II Borderline personality disorder. No other studies to the best of my knowledge have directly enquired after or investigated DYS in the setting of PWE.

**DEPRESSION IN PWE**

As much has been written about depression in PWE, but the time span (chronicity) was not commented upon in many cases, it may be prudent to examine depression in PWE to give us some idea as to the notion of DYS in PWE. As peri-ictal depression (that directly related to the ictus or seizure) is short lived, it will not be considered in this presentation, which will only discuss inter-ictal depression, which is by definition chronic, and not temporally related to the epileptic discharge.

**PREVALENCE**

Inter-ictal depression is the most common and clinically important affective disorder in PWE. It has been demonstrated that approximately 20% of patients with temporal lobe epilepsy (TLE) become moderately or severely depressed, and that 62% of patients with medically intractable complex partial seizures (CPS) have had a history of depression, of whom over a third (38%) satisfy criteria for MDD (see Robertson, 1992).

Indaco et al. (1992) documented that no less than a half of out-patients with epilepsy were depressed according to DSM criteria. Interictal depression prevalence can be deduced from clinical observations in addition to studies of psychopathology in PWE using a variety of standardised psychiatric rating scales, all of which have demonstrated that depression is increased in PWE, is higher than in controls, and several have reported higher depression scores for patients with psychomotor or TLE/CPS when compared to those with generalized seizures (see Robertson, 1988a, 1988b, 1992). Dodrill and Batzel (1986) suggested that the number of seizure types was more relevant to psychiatric problems in PWE than was the particular seizure type. Patients with TLE often have more than one seizure type and therefore, as a consequence, appear to be more maladjusted or psychiatrically disturbed.

As no studies have directly enquired about the prevalence of DYS in PWE, it is unknown as such, but may be somewhat deduced from the depression figures, and it may well be more common than hitherto recognised.
CHARACTERISTICS OF DEPRESSION IN PWE

Many studies have investigated specific aspects of the inter-ictal depression in PWE. Those investigations using rating scales, have documented that the majority of individuals were rated as reactive, non-endogenous or neurotic (e.g. Mulder and Daly, 1952; Edel and Toone, 1985; Robertson et al., 1987, 1994), in contrast to others (Betts, 1974; Mendez et al., 1986) who found more endogenous depression.

The severity of the depression seems to be moderate to severe, and features of depression are neuroticism, sadness, obsessionalism, dependence, altered sexual interest, paranoia, humourlessness, and an abnormal affect (Roy, 1979; Pilia and Harper, 1986; Robertson et al., 1987). Other characteristics of the depression in PWE include high anxiety (e.g. Roy, 1979; Betts, 1981; Perini and Mendius, 1984; Edel and Toone, 1985; Pilia and Harper, 1986; Robertson et al., 1987), anger (aggression, hostility) (e.g. Roy, 1979; Perini and Mendius, 1984; Perini et al., 1983; Robertson et al., 1987) and irritability (e.g. Brown et al., 1986; Mendez et al., 1986). In one study, Robertson et al. (1994) compared 18 general hospital out-patients with TLE, 18 DSM depressed out-patients, and matched normal controls. Results showed that depressive symptomatology, as measured by both self- and physician rated scales, was significantly higher in the TLE group than in the normal controls. However, most of the TLE group did not have MDD, in that only 4 (22%) met DSM criteria, and the depression scores were significantly lower than those of the psychiatric subjects with MDD. Moreover, all four of those TLE patients who met DSM criteria for MDD were also classified as non-endogenous.

Of added importance is that many depressed PWE patients have had previous neurotic (Roy, 1979) or depressive episodes (Pilia and Harper, 1986; Robertson et al., 1987).

Depressed PWE have often also been found to have had a significant previous history of depression, deliberate drug overdosage, and self harm (Roy, 1979; Pilia and Harper, 1986; Robertson et al., 1987) but others have found it not to be more so than a control depressed group without epilepsy (Mendez et al., 1986).

When one considers that DYS and neurotic depression are similar, it is of particular relevance that many of the depressed PWE had neurotic depression when specifically enquired after or measured using standardised instrument, rather than endogenous depression. Some of the characteristics of the depression were also not dissimilar to those in DYS, in particularly anxiety, anger and irritability. Therefore phenomenologically, some of the depressed PWE in the studies described may well have had DYS alone, or in addition to a MDD (as many satisfied MDD diagnostic criteria), in which case the PWE may have had “double depression”.

AETIOLOGY OF DEPRESSION IN PWE

Genetic Vulnerability

A genetic diathesis to depression may be important as several reports have indicated that a family history of depression or suicide is important in depressed PWE (Hancock and Bevilacqua, 1971; Brent et al., 1987; Robertson et al., 1987), while Mendez et al. (1986) failed to confirm this.
Dysthymia in Epilepsy

**Gender**

There has been some discussion as to whether gender may be important in the aetiology of depression in PWE. Depression in the general population is more common in females than males, (Bird and Harrison, 1987), and in depressed PWE populations this has also been reported to be the case in some (Palia and Harper, 1986; Robertson et al., 1987; Hermann and Whitman, 1989) but not other studies (Fenton, 1986; Mendez et al., 1986), in which men predominated. Altshuler et al. (1990) found that a left TLE depressed group (vide infra) had an insignificantly larger number of males and left-handed subjects. No sex differences for the occurrence of depression in PWE were reported by Victoroff et al. (1990).

**Psychosocial Factors**

Several psychosocial models of depression have been suggested (see Robertson, 1988b) and some of these may apply to PWE. Many investigators have discussed the stigma and social prejudice to which PWE are subject, while others suggest that PWE do not necessarily feel stigmatized (see Robertson 1988a, 1998b). Several investigations have found that PWE have a substantial number of psychosocial problems at school, in emotional, interpersonal, vocational, and financial matters; they show an increase in stressfull life events and family discord and also have problems coping with epileptic attacks; they have a poor adjustment to seizures, at least some of which stemmed from poor seizure control, caused by poor compliance with antiepileptic drug (AED) medication, lack of self esteem, inability to accept a diagnosis of epilepsy, or not being willing to disclose the fact of having epilepsy to others (e.g. Beran and Read, 1981; Danesi, 1984; Danesi et al., 1981; Dodrill et al., 1984a, 1984b; Arnost and Hospodar, 1985; Fenton, 1986; Hoare and Kerley, 1991). Many of these variables have been found to specifically relate to depression in PWE (Palia and Harper, 1986; Brent et al., 1987; Hermann and Whitman, 1989). The case for epilepsy being a human analogue of the learned helplessness theory at depression (Seilgman, 1975; Abramson et al., 1978) has been persuasively argued by Hermann (1979). In a careful investigation, Hermann and Whitman (1989) demonstrated that increased stressful life events, poor adjustment to seizures and financial stress were predictive of increased depression in PWE.

**Neuroepilepsy Variables**

Neuroepilepsy variables may also be important aetiological factors seen in depressed PWE. Several studies have noted a reduction in seizure frequency prior to the onset of the lowered mood (e.g. Dougler, 1959/60; Flor-Henry, 1969), while others have found that depression was associated with an increase in seizures (Dodrill and Batzel, 1986). The majority of investigations have found that depressive symptomatology is not intimately related to epilepsy variables such as age of onset of epilepsy, the presence of an intracranial lesion, nor seizure frequency (Trimble and Perez, 1982; Mendez et al. 1986; Fralin et al. 1987; Kramer et al. 1987; Robertson et al. 1987; 1994; Roy 1979; Hermann and Wyler, 1989).

Several neuroepilepsy variables do, however, seem to contribute to the depression. Thus, CPS and TLE (Mendez et al., 1986; Robertson et al., 1987) and, in particular, left-sided lesions (e.g. Robertson et al., 1987; Altshuler et al., 1990; Victoroff et al., 1990; Strauss et al., 1982; Seidenberg et al., 1995) have been recently implicated in the depression in PWE. Whether this left-sided predominance is specific as suggested by some (Mendez et al., 1986; Altshuler et al., 1990; Victoroff et
al., 1990), or because the left hemisphere and fronto-temporal areas seem particularly vulnerable as far as psychopathology is concerned, as evidenced by studies on head injury, stroke patients, or, because when focal abnormalities are found, foci on the left side appear to be more common, is as yet not certain (Robertson, 1992).

The severity of the depression has been shown to correlate significantly with the duration of the epilepsy, and an association was found between CPS and a past history of depression (Robertson et al., 1987).

Some investigators have found no associations between mood and antiepileptic drug (AED) medication (Mendez et al., 1986; Altshuler et al., 1990), but these are the exception. The majority of studies have found that AED's do affect the mental state of PWE. Several AED's have been shown to be positively psychotropic (improve mood) such as carbamazepine (CBZ) (e.g. Trimble et al., 1980; Rodin and Schmaltz, 1984; Andrews et al., 1986; Robertson et al., 1987), valproic acid (VPA) (Emrich et al., 1984), lamotrigine (Smith et al., 1993). Phenobarbitone (PB), on the other hand, which continues to be prescribed widely (in, for example, the third or developing world) has been shown to affect mood adversely, being associated with depression, suicidal ideation and suicidal behaviour (Brent, 1986; Brent et al., 1987; Robertson et al., 1987; Smith and Collins, 1987; Barabas and Matthews, 1988; Victoroff et al., 1990). Vigabatrin has also been noted to alter mood adversely (Ring and Reynolds, 1990, 1992; Ring et al., 1990).

**Possible Aetiological Factors of Dysthymia in PWE**

The depression seen in PWE and DYS may also share some common aetiological factors, such as a genetic diathesis (WPA, 1994). In particular, however the AED medications may produce DYS, as they are given over many years and therefore their effects (advantageous) and adverse side-effects (e.g. depression, suicidal behaviour) are long lasting.

**MANAGEMENT**

The management of inter-ictal depressive phenomena should initially be directed towards the identification of a possible cause of the mood problem. For instance, several studies have indicated that a high seizure frequency interferes with psychosocial functioning, and may masquerade as depression.

Behavioral methods of decreasing seizure frequency ought to be considered, using biofeedback techniques, operant conditioning, and relaxation (see Robertson, 1988a). When considering psychotherapy in the treatment of PWE with depression, especially when one considers the psychosocial causes of mood changes and the literature on stigma and epilepsy, one may opt for supportive therapy or a combination of formal psychotherapy (such as cognitive, interpersonal, or behavioral approaches) and antidepressants, which, as recently shown, is more effective than either treatment alone (see Robertson, 1988a).

Assessment and rationalization of the patient’s AED medication is also important, and improvement in the mental status of patients with a reduction of polypharmacy, and discontinuation with PB has been reported (Shorvon and Reynolds, 1979; Thompson and Trimble, 1982).

If monotherapy is possible and all other factors, such as type of epilepsy, are taken into account,
CBZ would seem the most appropriate AED. This rationalisation of AED medication may also be one of the first options when treating potential DYS in PWE. What is the role of antidepressant medication in depression in PWE? Only two studies have addressed treating depression in this population, and none have studied the treatment of DYS in PWE.

Ojemann and colleagues (1983) undertook a retrospective case study on 19 depressed PWE and found that the tricyclic (TCA) doxepin (mean dose of 164 mg daily) improved the depression; in addition, the seizure frequency was reduced in the majority of patients, and increased in two. Robertson and Trimble (1985) reported on a double-blind placebo controlled study on 42 depressed PWE comparing amitriptyline and nomifensine. At six weeks the majority of patients responded significantly and there were no significant differences between the two drugs and placebo; at 12 weeks nomifensine was superior to amitriptyline. Of note is that there were no clinically significant differences in seizures between the drugs.

It is well known that virtually all non-monoamine oxidase inhibitor (MAOI) antidepressants lower the seizure threshold (Trimble, 1978). Medications most likely to be implicated with seizures are amoxapine, bupropion, chlorimipramine, maprotiline, mianserin and trazodone. Drugs which are less likely to be associated with seizures and which are therefore probably safer, are the MAOIs, doxepin, viloxazine, protriptyline, butriptyline, and the SSRIs fluoxetine, fluvoxamine, paroxetine and sertraline (Edwards, 1985; Edwards and Wheal, 1992; Rosenstein et al., 1993).

To the best of my knowledge, no seizures have been reported in association with the new MAOI (RIMA), moclobemide, which is safer than the “old” MAOIs, and this may well be the antidepressant of choice in depressed PWE. Moreover, it has been demonstrated that moclobemide is relatively free of psychomotor and cognitive impairment (Hindmarch and Kerr, 1992), which are characteristic of TCAs, and this is further reason for prescribing moclobemide in PWE. SSRIs are also less sedative than the TCAs.

Non-sedative antidepressants in this PWE population are an important consideration, as the ADEs which the patient will be taking may have sedative side effects. Many clinicians, however, prefer to use antidepressants they know well, and commence with small doses, increasing the dose gradually (see Robertson, 1988a, 1988b). One should discontinue the antidepressant if there is an increase in seizures, and the patient should be admitted to hospital if there is a resultant poor seizure control or a risk of status.

One should also regularly monitor AED levels regularly, as they are usually affected by antidepressant drugs. For example, phenytoin levels may be increased by imipramine, nortriptyline and viloxazine (Perucca and Richens, 1977), while CBZ toxicity has been caused by viloxazine (Pisani et al., 1984, 1986).

As suicide and parasuicide are common in PWE (Mackay, 1979; Barraclough, 1981; Mathews and Barabas, 1981), safer antidepressants in overdose (e.g. SSRIs) should probably also be prescribed. Finally, as the relationship between depression and epilepsy is complex, the treatment, which can also be complex, is best handled by someone well versed in both disorders.

If one diagnoses DYS in PWE, and antidepressant medication is considered, the above principles should be adhered to, bearing in mind that in DYS, MAOIs (e.g. phenelzine), RIMA (moclobemide), TCAs (e.g. amitriptyline, imipramine) and the SSRIs (e.g. fluoxetine) have been demonstrated to be useful (Hirschfield, 1994; WPA, 1994).
CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

DYS in PWE has received scant attention in the literature, with only two studies mentioning DYS specifically. Thus, the true incidence, prevalence and phenomenology and treatment of DYS in PWE are unknown quantities. Depressive symptomatology and MDD in PWE have been documented and some of the patients described may well have had DYS. This is particularly so, as some aetiological factors in the depression described in PWE include AED medication, TLE/CPS and lifelong social stigma (i.e. all chronic factors), as opposed to life events (which are phasic) and which often contribute to MDD, and therefore some of what has been written about depression in PWE may be extrapolated to describe DYS in PWE. In addition, early original clinical observations about depression in PWE discussed neuroepilepsy and seizure variables, such as the reduction in seizure frequency (Dongier, 1959/60) and right temporal lobe lesions being associated with manic depressive disorder (Flor-Henry, 1969). Many of the subsequent studies in the area have therefore concentrated on the neuroepilepsy variables, aetiological factors etc., rather than describe the phenomenology and treatment of the depression. Future studies are suggested to examine the prevalence, phenomenology (e.g. separating for example mood disorders into DSM IV and MDD), examining the aetiology (e.g. biological factors in the context of the separation) and the treatment of DYS in PWE.

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DYSTHYMIA AND EPILEPSY IN DEVELOPING COUNTRIES

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Service de Neurologie
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INTRODUCTION

Epilepsy, being a chronic disorder, represents a serious public health problem in developing countries. The prevalence is between 8,000-24,000 in several African countries; it is therefore important to keep in mind the social impact of sociocultural prejudice related to epilepsy (Ndiaye et al., 1983; Osuntokun et al., 1987; Karfo, 1991). Lack of appropriate medical information can cause a hostile environment towards patients with epilepsy, further worsening the psychosocial morbidity of epilepsy.

Unfortunately, most of the studies performed in developing countries are particularly related to clinical aspects, therapeutic assessment, and epidemiology, and few investigators have focused on the psychosocial sequelae of epilepsy in developing countries. Studies on the psychological aspects are therefore essential (Giel, 1967; Terranova and Ratsifandri, 1970; Danesi et al., 1981; Gureje, 1991; Tekle Haimanot, 1992).

Here we report the results of a study on the dysthymia in patients with epilepsy in a developing country: Senegal.

PATIENTS AND METHODS

The present study represents a prospective study to understand dysthymic disorder during epilepsy.

Reports include 197 patients, 129 men and 71 women, all of them from Black Africa, ages 15-45 years, studied at the clinic of the University Hospital Center of Fann in Dakar. Patients in the study had epilepsy for at least two years and without specific cause such as brain tumor, head trauma, cerebrovascular disorder, infectious disorders due to bacteria, virus, or parasites.
Table 1: Following sex and age (3)

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-25</td>
<td>74</td>
<td>30</td>
<td>104</td>
</tr>
<tr>
<td>26-35</td>
<td>32</td>
<td>26</td>
<td>58</td>
</tr>
<tr>
<td>36-45</td>
<td>20</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>Total</td>
<td>126</td>
<td>71</td>
<td>197</td>
</tr>
</tbody>
</table>

Regarding the electrophysiological classification, we follow the criteria of the International League Against Epilepsy, with 169 grand mal seizures, 28 focal seizures, 14 temporal seizures, 8 motor and 6 sensitive seizures. In terms of treatment, monotherapy was prevalent in 176 patients (89.34%) with efficacy of treatment in 81% of cases.

Table 2: Type of Treatment

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Total = 176</th>
<th>Polytherapy</th>
<th>Total = 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Nr. of patients</td>
<td>Drug</td>
<td>Nr. of patients</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>143</td>
<td>Phenobarbital and Phenytoine</td>
<td>9</td>
</tr>
<tr>
<td>Phenytoine</td>
<td>14</td>
<td>Phenobarbital and Carbamazepine</td>
<td>7</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>11</td>
<td>Phenobarbital and Sodium Valproate</td>
<td>3</td>
</tr>
<tr>
<td>Sodium Valproate</td>
<td>8</td>
<td>Phenobarbital and Carbamazepine and Clonazepam</td>
<td>3</td>
</tr>
</tbody>
</table>

In this study the biographical information (sex, age, social status) and the therapeutic information (nature, duration) were obtained at the time of the initial clinical evaluation for study participation. For this study, dysthymia was assessed as defined in DSM-IV. Dysthymia and its clinical manifestations related to affective disorder were systematically investigated, with particular attention paid to the following symptoms:

- insomnia or hypersomnia
- strength loss or chronic fatigue
- feelings of inadequacy, loss of self-esteem and self-depreciation
Dysthymia and Epilepsy in Developing Countries

- Decreased efficiency in school, at work, and at home
- Diminished attention, concentration, and ability to think clearly
- Loss of interest in pleasure and agreeable activity
- Irritability and excess overreactivity
- Incapacity to respond to pleasure, compliments, or offer reward
- Less active, withdrawn, deterioration of behavior in social environments
- Pessimistic attitude towards future events and ruminations of past events
- Crying
- Recurrent thoughts of death and suicide

RESULTS

35 out of 197 patients with epilepsy presented clear dysthymia. Specifically, 22 men and 13 women, ages between 15 and 25 years, in 24 cases from 26-35 years old, and in 8 cases from ages 36 to 45 years.

Table 3: Frequency of dysthymia as a function of sex

<table>
<thead>
<tr>
<th>Sex</th>
<th>Epilepsy total</th>
<th>Dysthymia and Epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>126 (63.96%)</td>
<td>22 (17.46%)</td>
</tr>
<tr>
<td>Female</td>
<td>71 (36.04%)</td>
<td>13 (18.30%)</td>
</tr>
<tr>
<td>Total</td>
<td>197 (100%)</td>
<td>35 (17.76%)</td>
</tr>
</tbody>
</table>

From the point of view of electrophysiology, 35 cases were related to grand mal seizures, 23 to focal seizures, 12 to temporal seizures, 4 to motor and 3 to sensitive seizures.

In terms of therapy, patients had been treated for 3 years with monotherapy with phenobarbital in 30 cases (20.98% of 143 epileptics with phenobarbital only) and with carbamazepine for temporal/focal seizures in 5 cases (45.5%) of 11 cases treated with carbamazepine alone.

Regarding clinical symptoms, we observed in our population of 35 epileptics with dysthymia physical/intellectual asthenia which was chronic, anorexia, insomnia, feelings of self-depreciation. Two patients treated with phenobarbital presented at the same time insomnia with hypersomnia during the day.

Other manifestations of dysthymia we observed were:
- Feelings of despair in 20 cases
- Tendency to isolation in 10 cases
- Irritability with hyper reaction in 7 cases
- No suicidal tendencies found

Cognitive disturbances like memory loss and difficulty in learning have been observed in 18 patients who were treated with phenobarbital.
DISCUSSION

Variations in socio-economic status (SES) among our patients was not a confounding variable because they all had the same SES (disadvantaged).

Age, sex, or type of therapeutic intervention did not influence the outcome of dysthymic disorder in our study. The predominance of women observed in our series is normal in our country and superimposable to the general statistic that men go more frequently to consultation and frequent hospitals.

Temporal location of the seizure seems to be an important factor as 45.45% of epilepsy patients with dysthymia had been treated with carbamazepine. From a clinical standpoint, dysthymic disturbances are more frequent during focal epilepsy in 12 out of 28 cases with frequency of 53.57% with temporal, 37.71% being seen in other studies. (Currie et al., 1971; Mendez et al., 1986; Robertson et al., 1987; Robertson et al., 1992; M’Boussou, 1981).

Symptoms of chronic fatigue, insomnia, anorexia with feeling of self-depreciation were always observed in our sample and were the clearest clinical symptoms. No suicide attempts have been noted in contrast to observation (Mendez et al., 1986; Stevenson and King, 1987) that considers the outcome of depression in an epileptic as a risk factor for suicide. In addition, no sentiments of profound guilt have been observed. In general, suicide attempts are very rare in the course of depression in Black Africa (Altshuler, 1990; Septien et al., 1993). No sense of pathological guilt has been evident in our patients with dysthymia and epilepsy.

The chronicity of epilepsy along with the need to take daily medication for prolonged time and the sociocultural stigma seem to predispose epileptic patients to dysthymia. The rate of 17.76% of dysthymic disorder (35 cases of dysthymia among 197 patients with epilepsy) may seem small in comparison to other studies, reporting frequencies between 20% to 62%.

However, it must be noted that in general, affective illness is less frequent in Black Africa than in industrial countries.

SUMMARY

Epilepsy is a serious public health problem. Limited attention has been given to psychosocial aspects of epilepsy in Sub-Saharan Black Africa. The interpretation of the sociocultural aspects and stigma of the disease has an important impact on the degree of morbidity of epilepsy. Among 197 epileptic patients (126 men and 71 women), 35 cases of dysthymia were reported using DSM-IV criteria, representing a frequency of 17.6%.

Dysthymia has been seen particularly during partial epileptic seizure (in 53.57% of patients) and in temporal epilepsy (in 37.7% of patients).

Age, sex, nor type of treatment, even monotherapy with phenobarbital do not influence the emergence of dysthymia in patients with epilepsy. The predominant features of dysthymia in our population as insomnia, anorexia, chronic fatigue as well as sentiments of self-depreciation are constantly observed. We did not observe extreme guilt or suicide feelings or attempts. In conclusion, it is important to determine whether during the course of epilepsy, depression or dysthymia are present.
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FEATURES OF DYSTHYMIA AND PSYCHOTHERAPY

Dysthymia is a psychiatric disorder in which treatment with psychological intervention or psychotherapy seems to be the first choice due to several reasons (see Table 1). Dysthymia is a mood disorder of moderate severity. As there is general consensus in the literature that psychotropic drugs are the primary treatment in severe or melancholic subtypes of depression, there is at least some discussion whether this similarly applies to depression of moderate or mild severity (Paykel et al., 1989). On the other hand, the efficacy of psychotherapy has always been questioned in severe cases (Thase et al., 1996) but undoubtedly has a place in the milder forms. Here psychotherapy is seen as similarly effective if not even more effective than drug treatment (Blackburn, 1984; Hautzinger et al., 1996a).

Dysthymia is also by definition a chronic disorder. This means that a general behaviour style is present in which depression can no longer be as easily contrasted with normal phases as in episodic courses. Not surprisingly, therefore, dysthymia is historically the successor to depressive personality or character disorders (Kocsis and Frances, 1987; Hirschfeld, 1990).

Table 1: Features of dysthymia speaking for and/or leading to psychotherapy

<table>
<thead>
<tr>
<th>Low to moderate intensity of the depressive syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>- questionable drug efficacy in milder forms of depression</td>
</tr>
<tr>
<td>- primary indication for psychotherapy in milder forms of depression</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chronicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>- similarity between dysthymia and neurotic or personality disorder</td>
</tr>
<tr>
<td>- adaptation disorder</td>
</tr>
</tbody>
</table>

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<tr>
<th>Feasibility and practical aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>- illness concepts and treatment expectations of patients</td>
</tr>
<tr>
<td>- non-recognition as mood disorder by physicians</td>
</tr>
<tr>
<td>- enough time to organize psychotherapy</td>
</tr>
<tr>
<td>- contraindications for drug treatment</td>
</tr>
</tbody>
</table>
It can no longer be as easily discerned as to what must be attributed to “illness” and what to “structure”. As personality disorders, developmental disorders or neurotic disorders have since long been regarded as the primary target for treatment by psychotherapy (Bemporad, 1976), dysthymia can therefore also be seen as a primary candidate for psychotherapy. Finally, it must be realised that in chronic disorders there is a higher risk of secondary negative adaptation problems than in acute and short episodes (Paykel and Weissman, 1973; DeLisio et al., 1986; Cassano et al., 1990). If a patient is more or less depressed for longer periods of time, if not even from childhood onward (Kovacs et al., 1994), inevitably his social behaviour and social network will change; success in the professional area will be affected, pleasure in recreational activities will be reduced, and the perception of a patient of and by his environment will be altered. Thus, secondary problems in many life areas will arise which also seem to be important targets for psychotherapy (Markowitz, 1993).

There are also practical aspects which can make psychotherapy a first choice in dysthymia. The fact that dysthymia is embedded in characterological, psychological and social problems creates additional difficulties. Patients will develop interpretations of their condition as a psychosocial problem, whatever the “real” nature of cause may be. This can foster the assumption that psychotherapy instead of drug therapy is the proper choice of problem-solving (Linden, 1987).

Similarly there is a risk that also physicians will not recognize such disorders as depressive illnesses but rather see them as stress related problems and therefore also recommend psychotherapy as first choice treatment (Howland, 1993; Rost et al., 1994).

Also chronicity has a very practical aspect with respect to treatment selection. Psychotherapy may be difficult to implement in acute episodes because some time of preparation is necessary, e.g. because the patient must submit an application to his medical insurance for reimbursement or because he must find a specialized therapist. In chronic disorders the patient’s preparations and the fulfilment of organisational requirements present no problem. Patients undergoing standardised forms of psychotherapy in the general health care field are therefore in their majority suffering from depressive disorders of longer duration (Linden, 1996).

Finally, there may be contraindications for drug treatment, especially when it comes to long-term treatment as may be necessary in many dysthymic disorders. In such cases psychotherapy can be a valid alternative choice.

**PSYCHOTHERAPY GOALS AND THE PSYCHOTHERAPEUTIC PROCESS IN DYSTHYMIA**

In attempting to specify what psychotherapy can achieve in dysthymia, reference must be made to psychological theories on the aetiology and development of depression. There are at least four major models which are also directly related to treatment approaches (Figure 1). They can be summarised as the mood model, cognitive model, coping model, and stress model (Linden, 1987a).

In dysthymia, mood is by definition lowered and impaired. Whatever the cause of depressed mood may be, there is evidence that depressed mood has a number of negative consequences (Cassano et al., 1990). Changes in mood are associated with changes in cognition, e.g. selective perception and memory or interpretation of the self or the future (Singer and Salovey, 1988; Mackie et al., 1992). Coping behav-
ior is also influenced by mood, since drive or trust in oneself is changed or even cognitive functioning can be impaired in depression (Reischies et al., 1992). Finally, negative mood will lead directly to negative changes in the individual's living condition, through the induction of negative mood and also critical behaviour in others and the impairment of social competency in general (Hautzinger et al., 1982).

The cognitive model explains depression by proceeding from negative and dysfunctional cognitive schemata (Beck et al., 1979). If an individual holds chronic negative beliefs, e.g. of the type that he or she is inadequate by virtue of personality or that regardless of the circumstances a negative outcome is most likely, coping abilities can be impaired, and negative consequences as a self-fulfilling prophecy can in many social situations lead to negative consequences and strain. Career success and loving relationships can be endangered. Finally, mood itself will be hampered if everything is seen in a negative perspective. Validity for this does not only come from clinical and psychological observations but also from psychophysiological or PET studies, which have shown that imaging of negative memories not only leads to subjective feelings of dysphoric mood but also changes in covert facial electromyographic activity (Schwartz et al., 1976) or cerebral blood flow changes in inferior and orbitofrontal cortices (Pardo et al., 1993).

The coping model proceeds from the assumption that a lack of social skill, interpersonal competence or coping behaviour in general will lead to problems in social relationships and social adaptation and to concomitant social strain (Hersen et al., 1984; Klerman et al., 1984). Incompetent behaviour will also result in frustration, in inability to get needed reinforcers, and in the long run in mood impairment. Finally, repeated failure in coping situations will also generate negative self-perceptions and negative expectations about the future.

The stress and social strain model sees chronic and especially unavoidable uncontrollable over-

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**Figure 1: Psychological models of depression and dysthymia**
taxation or repeated uncontrollable negative life events and stressors at the beginning of depression (Seligman, 1975). Chronic burdens are seen as causing feelings of giving up, despair and helplessness. Helplessness and hopelessness in particular are not merely emotions but are also cognitions, i.e. interpretations, expectations, and attributions of not being in control. Even in animal experiments it has been shown that chronic exposure to unavoidable adverse stimulation impairs the ability to cope with relevant situations even when control is possible (Hellhammer, 1983).

These basic models of the psychology of depression can easily be integrated in a single multidimensional systemic model in which mood, cognition, coping behaviour, and social strain can exert mutual influences on each other. Bad mood can generate interpersonal problems which in turn will be felt as a burden and will impair mood themselves. Negative beliefs and expectations of helplessness can be the consequence and simultaneously be the cause of reduced ability to cope with demands of daily life, which in turn will generate additional problems and strains, negative mood and negative cognitions. Psychotherapeutic interventions will therefore always look at all these components of the depressive syndrome simultaneously and attempt to intervene in this vicious cycle, which not only can generate depressive states, but also foster chronic developments and hinder recovery.

The field of behaviour therapy disposes over many kinds of psychotherapeutic intervention which can assist to overcome adequate interpersonal skills and improve coping behaviour in general (Linden and Hautzinger, 1996). Assertiveness and social competency training (Becker and Bellack, 1987) teach how to engage in fruitful and positive social relationships. Role playing and home work assignments are examples of related techniques. They are also used in problem-solving approaches (Marchione, 1985) which aim at assisting the patient to get out of stressful life situations or to prevent the development of chronic life strain. The primary strategy in this therapeutic technique is to divide global problems into small segments and detailed problems which are small enough for the patient to be handled and to allow successful coping behaviour.

Modification of dysfunctional cognitions has been the primary focus of cognitive therapies, as they were originally developed in the context of depression (Beck et al., 1979). This treatment approach typically starts by identifying automatic thoughts which are then grouped into cognitive schemata or basic beliefs. The patient is then guided in learning how such interpretations and expectations of the world influence mood and behaviour. And, finally, these dysfunctional cognitive schemata are modified. Psychotherapeutic techniques are self-observation, cognitive rehearsal, or internal dialogue.

Psychoanalytically oriented treatment approaches also try to change interpersonal bonding, role behaviour, perception of oneself and others, or transference (Jacobson, 1971; Arieti and Bemporad, 1978). A modern approach emerging from this background, resembling in many aspects cognitive and behavioural approaches, is the interpersonal psychotherapy of depression (IPT) (Klerman et al., 1984). In IPT factors which are sought contribute to the patient’s depression here and now; current stress factors are identified, key persons involved in current disputes and disappointments, as well as the patient’s coping style and his assets. IPT helps the patient to ventilate painful emotions, talk about situations that evoke guilt, shame, or resentment, clarify wishes, and possibly find satisfying alternatives.

Only few psychotherapeutic approaches focus directly on changing mood and anhedonia. One example is euthymia therapy or pleasure and hedonia training (Laux, 1988). This strategy begins by teaching patients sensual experiences on all stimulus levels. Patients are guided to smell or taste,
consciously observe light and shadow or different colours, and feel different textures, thereby altering perceptual input in general.

**CLINICAL STUDIES ON THE EFFECTIVENESS OF PSYCHOTHERAPY IN DYSTHYMIA**

The above briefly summarized psychotherapeutic theories on depression have a certain face validity. They propose interesting and helpful ways in approaching depressed patients even in daily clinical work. Counselling and guidance of patients are part of any therapeutic encounter and can be professionalized further by referring to the theoretical concepts described above. In addition to their scientific foundations, psychodynamic, interpersonal, cognitive, and behavioural concepts all are also based on the clinical experience of their authors. It is therefore recommended that clinicians refer to such psychological descriptions of depression in order to better deal with these disorders. On the other hand, however, it must not be forgotten that an inappropriate psychological explanation of depressed mood can also have undesirable effects if the patient inappropriately learns to regard himself as responsible for his negative state, which by “blaming the victim” loads additional burden on the patient (Cooper, 1985). Problem and coping-oriented approaches may carry with them this risk to a lesser extent than interpretative methods.

Another problem is the question as to whether any of these psychotherapies can claim proven efficacy in the treatment of depression, particularly dysthymia. Sound evidence is now available that several forms of psychotherapy are effective in the treatment of acute depressive episodes of moderate severity, preferably in outpatients but also in inpatients (Hautzinger, 1993). To date only a limited number of studies has been conducted on the treatment of dysthymia.

Although it has been repeatedly claimed that psychodynamic and psychoanalytic psychotherapy is the treatment of choice for depression and especially chronic depression (Jacobson, 1971; Bemporad, 1976) no empirical outcome data, neither on acute episodes nor chronic disorders, have been produced to date (Markowitz, 1994).

Interpersonal psychotherapy has been shown to have clinically meaningful effects in the treatment of major depression and even prophylactic effects against recurrent major depression. (Elkin et al., 1989; Frank et al., 1990). Interpersonal psychotherapy has therefore been recommended for treatment of dysthymia as well (Weissman and Akiskal, 1984; Cassano et al., 1990). Markowitz and Klerman (1993) prepared a special Manual of Interpersonal Therapy of Dysthymia, proposing adaptations of the treatment of this chronic personality-like disorder, assuming that the patient has to undergo an “interpersonal role transition” from a chronically depressed style into euthymia. Markowitz (1994) reports three pilot trials with IPT on a total of 17 patients. This approach produced changes in the Hamilton Depression Scale score from about 20 at the beginning of treatment to about 8 at the end of treatment. Several of the treated patients had earlier failed to respond to vigorous drug treatment (Mason et al., 1993).

Also for cognitive behaviour therapy, research groups internationally have gathered multiple evidence that this represents an effective mode of treatment in major depression (Hautzinger, 1993; Wright et al., 1993). In addition there are a few trials which focus more or less specifically on dysthymia. Stravynski et al. (1991) reported for 6 patients a drop in the Hamilton score from 24 to
9 after treatment and a score of 8 six months later. McCullough (1991) reported on the treatment of 10 patients who showed Beck Depression Inventory scores of 10 or less after 31 weekly sessions on average, with 9 patients still in remission two years later. Mercier et al. (1992) treated 15 dysthymic patients in a trial on atypical depression. Six out of 15 patients with dysthymia responded according to global clinical impression rating. Hautzinger et al. (1996a) reported on a study with 191 “neurotic” non-melancholic depressed patients. This group contained 19.6% dysthymia cases. They were randomly assigned either to cognitive behavioural therapy, antidepressant treatment or a combination of both. Patients came from inpatient and outpatient settings. All three treatment modes showed comparable and significant reductions in several outcome measurements. The Hamilton score fell from about 24 to 9. Full responders with both a Beck Depression Inventory score and a Hamilton score of 9 or less comprised 34% of the antidepressant group, 41% of the cognitive behavioural therapy group and 48% of the combination group. The authors do not report special analyses on dysthymia patients but split their statistics according to severity. They found no difference in treatment results in the more severely as compared to the less severely depressed patients. When performing exploratory analyses on predictors of response, patients with a longer duration of the depressive episode tended to have higher depression scores at the end of treatment (Hautzinger et al., 1996b).

Finally, several additional miscellaneous psychotherapy studies have been conducted, as that by Roller and Lankester (1987), in which for the most part dysthymic patients were treated with group therapy including Gestalt techniques (e.g., the empty chair technique or paradoxical interventions), by Udeman and Udeman (1985) using unspecified supportive psychotherapy, and by Waring et al. (1988) using marital therapy. The reports on these studies all claimed positive clinically relevant changes. Euthymia therapy should also be mentioned because of its interesting and unique theoretical approach. There are reports on several small trials with so-called “psychosomatic patients” also claiming valuable treatment results (Koppenhöfer, 1990; Lutz, 1996). Although to date dysthymia has not been addressed directly, euthymia therapy nevertheless seems to be a psychotherapeutic approach with special pertinence to this disorder.

CONCLUSIONS AND RECOMMENDATIONS

Empirical data to date are not sound enough to prove that psychotherapy of any type is effective in the treatment of dysthymia (Markowitz, 1994; Paykel, 1994). There is also some evidence that chronicity is a predictor of insufficient outcome (Fennell and Teasdale, 1982; Hautzinger et al., 1996 b; Leung and Orrell, 1993), so that results from the treatment of acute episodes cannot be directly transferred to the treatment of chronic disorders. Furthermore, there are no good data which would allow a comparison of treatment efficacy among different modes of treatment, especially drug treatment. This would be particularly important for the comparative evaluation of differential treatment indications.

Nevertheless, several reports on promising clinical experience suggest that interpersonal psychotherapy and cognitive behavioural therapy can be useful in the treatment of dysthymia. Available results justify larger treatment trials with more rigorous methodology and control groups including proper pharmacological treatment. In any case, psychotherapy seems to be indicated as a treatment option particularly if other modes of treatment, e.g. with drugs, have not been feasible or have been
shown to be ineffective. This implies a model of sequential decision-making in the treatment of depression or dysthymia (Linden, 1995a) which allows to give the following recommendations:

1. Treatment selection (e.g. different types of psychotherapy or pharmacotherapy) should be guided first by availability. A method of treatment which cannot be carried out properly in a given treatment setting must be postponed.

2. Treatment feasibility should be the next decision criterion. Costs or tolerability and contraindications can govern the decision against one option and speak in favour of the other.

3. Treatment orientations and expectations of patients constitute the next important aspect in treatment selection. In the case of psychotherapy it is obvious that unwilling patients are not good partners and that this will endanger treatment response. Thus, other treatment options, such as pharmacotherapy, should be considered first. The same has been reported for drug treatment (Rickels, 1968; Linden, 1995b). Patients who are opposed to drugs will drop out of treatment more easily and if they stay in treatment will have poorer response rates.

4. Treatment history should guide treatment selection in the next step. A treatment mode which has worked in the past should be the first choice in a new treatment episode, whereas a treatment which earlier produced intolerable side effects or non-response should not be chosen again.

5. If treatment of one type has been started and has yielded a partial response treatment combination should be the next step. It has been discussed that pharmacotherapy and psychotherapy work through complementary mechanisms, so that medication will directly influence mood regulation but not social skills and vice versa for psychotherapy. Therefore, it is theoretically conceivable that some patients would rather be treated with one or the other. Also some patients need treatment on different intervention levels at the same time. Partial response could be a clinical indicator for this kind of combination.

6. If there has been non-response to one treatment in the present episode patients should be offered the alternative treatment approach in the next step. After drug failure psychotherapy still offers the possibility for improvement, as suggested in e.g. the report by Mason et al. (1993). The same is true for patients who did not respond to psychotherapy as a first step. Here also a shift to drug treatment can open new response options (Stewart et al., 1993).

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Psychological Treatment of Dysthymia


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INTRODUCTION

Chronic minor depressions and dysthymic states were initially considered to depend from a character neurosis, therefore the treatment of choice was psychotherapy. Although monoamine-oxidase inhibitors (MAOIs) were claimed early to be effective in patients with «atypical» depression (West and Dally, 1959) or in neurotic patients (Tyrer, 1976), a major conceptual change was introduced by DSM-III when dysthymia was classified in the affective disorders section. Current results of drug therapy in such patients remain puzzling both for practical and theoretical reasons.

Chronic depression, whether patients fulfill criteria for major depression or not, is frequent in psychiatric settings (Keller and Shapiro, 1982; Rounsaville et al., 1980) representing a proportion of a quarter to a third of depressed patients. Dysthymic patients do consult their general practitioners (GPs) as shown in the World Health Organisation (WHO) study conducted in 14 different countries (Goldberg and Lecrubier, 1995), in this study the prevalence of dysthymia among 25,916 consecutive presenting patients was 2.1%. It is interesting to note that the percentage of patients recognised as psychiatric cases (59%) was higher than for other disorders, probably due to two factors: 1) the chronicity of dysthymia leading to numerous consultations; 2) the high disability induced by this disorder. The proportion of patients with moderate to severe disability was 52% in dysthymites as compared to 57% in major depressed. In both depressive disorders, patients had a mean number of eight disability days during the past month. This symptomatically mild disorder is therefore severe both at the patient and at the socio-economic level. This underlines the importance of recognising and treating dysthymic patients. In clinical settings, the coexistence of dysthymia and major depression is high since dysthymic patients consult more frequently when their symptomatology worsens. In GP settings (WHO study), the comorbidity was 50%; in psychiatric settings the figure is usually close to 75%. In addition, these comorbid patients have been reported to have poor outcome or to experience incomplete recovery (Weissman and Klerman, 1977; Bronisch et al., 1985).
Initial trials conducted in patients with mild chronic depressive states according to RDC already suggested that dysthymic could benefit from drug treatment. This was confirmed by numerous double blind trials performed in dysthymic patients. Moreover dysthymia is a chronic disorder and there is good evidence that these patients need long term maintenance therapy (Kocsis et al., 1995; Versiani, 1996). The reference drugs, tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs), are either poorly tolerated or pose safety problems, therefore their benefit risk ratio for long term treatment needs improvement. In addition compliance is a major factor for long term therapeutic success and although good tolerance is not the unique important variable to improve compliance it is certainly a major factor. The next pages will describe the results observed for drug treatment in chronic minor depression or dysthymia and different attempts to develop new compounds effective and well tolerated.

**OPEN TRIALS CONDUCTED IN CHRONIC MINOR, INTERMITTENT DEPRESSION (RDC) OR DYSTHYMIC PATIENTS (DSM)**

Before the concept of dysthymia was introduced in DSM-III most trials were conducted in patients with chronic minor or intermittent depression according to RDC (Spitzer et al., 1978). Many uncontrolled studies explored the efficacy of drug therapy in these «minor» depressive conditions providing valuable information due to their design and the careful evaluation of evolution under treatment.

Akiskal subdivided a group of 137 dysthymic (DSM-III) patients into characterological depression, chronic primary depression and secondary depression. Drug treatment response was positive in two third of chronic primary depressives and in only one third of patients with characterological or secondary depression. EEG sleep variables suggested that the group of primary depressives was close to patients with unipolar depression.

An heterogeneity of response to pharmacotherapy according to clinical variables was also suggested by Keller. They compared the response to antidepressants of patients with major depression or chronic minor depression with a superimposed major depression (double depression). A high good response rate was observed in both groups as for improvement of the major depression but in the group of double depression only 31% had recovered from both conditions after one year and 39% after two years.

A similar result was found by Klein after six month treatment of double depression (25% responders), or major depressives (68% responders) using DSM-III criteria. As in Akiskal’s studies Klein also found the age of onset to influence the response to pharmacotherapy. The percentage of responduers after six month treatment was 23% in the early onset group and 44% in the late onset group.

Specific serotonin reuptake inhibitors (SSRIs) have been reported to be effective in the treatment of major depression (Boyer et al., 1991) due to their good tolerance they appear as a potential treatment for chronic affective disorders. In addition to case reports some open studies suggested SSRIs to be effective. Akiskal (1996) indicates preliminary evidence that fluoxetine in combination with lithium or thyroid supplementation have a long term (at least two years) beneficial effect in 80% of dysthymic patients. Ravindran et al. (1994) evaluated the response of 52 primary dysthyminics...
to fluoxetine after six weeks treatment. The overall response rate was good with 73 responders (HAM-D reduced ≥ 50%); results in the subaffective subgroup (77% responders) were better than in the character spectrum group (25% responders). A higher anxiety level was associated with a poorer response to treatment. Other authors also studied the response of chronically depressed to antidepressants but either the proportion of patients likely to be dysthymics is difficult to evaluate (Ward et al., 1979; Garvey et al., 1989) or the sample size is very small (Rihmer et al., 1983; Corona et al., 1989), or treatment was not provided to all patients and criteria for treatment response are unclear (Barrett, 1984).

Overall the open studies provide some evidence that antidepressants may be a useful treatment of chronic minor or dysthymic patients. They also suggest that minor depression/dysthymic patients show a lower good response rate to pharmacotherapy than major depressives. However, no specific treatment is really explored in these studies and different substances at different dosages were prescribed in most of them and this makes even more difficult to interpret the results.

**DOUBLE BLIND COMPARISONS CONDUCTED WITH MAOIS IN CHRONIC MINOR OR INTERMITTENT DEPRESSION LIKELY TO INCLUDE DYSTHYMIC PATIENTS**

Most of these studies were conducted in patients with minor (mD) or intermittent (ID) depression according to RDC (Spitzer et al., 1978). In the studies selected, the chronicity of the patients renders the diagnosis of dysthymia likely but not certain. Rounsaville et al. (1980) studied the response of four groups of patients to amitriptyline or perphenazine, these were major depression (MDD), chronic intermittent depression (CID) and MDD, cyclothymic personality and labile personality and MDD. All diagnostic groups responded to treatment although, due to the relatively small size of the sample (64), the effect of each specific treatment was not analysed. Tricyclic antidepressants and MAOIs were also compared in a double blind study versus placebo by Quitkin et al. (1989). The main interest of authors was the response of depressed with atypical features to phenelzine, imipramine or placebo. Approximately half the sample had MD or ID and most patients were chronically depressed. Both active drugs appeared to be superior to placebo after 6 and 12 weeks treatment and phenelzine was found superior to imipramine. However the atypical features possibly influenced this result. On the contrary, in a sample of MDD and mD with atypical depression, Davidson et al. (1988) found isocarboxazide, another MAOI to be effective in MDD but not in mD.

In a sample of MDD, mD and ID with low scores on the HAM-D (< 19) Guy et al. (1983) compared mianserin to placebo. Patients were classified according to Klein (1974) into endogenomorphic depression, dysphoria or disappointment reactions. Endogenomorphic and chronic dysphoric patients responded better to mianserin than to placebo while the contrary was true for patients with a disappointment reaction. In this study dysthymia is a probable diagnosis for the group of chronic dysphoric patients. A negative result was found by Paykel et al. 1988 in a placebo controlled trial comparing amitriptyline to placebo in MDD, mD and ID. The response to amitriptyline observed in patients with MDD was better than the placebo response. No difference was observed in MD and ID. Patients with scores lower or equal to 13 on the HAM-D had a better response to the active drug. It is not clear whether the diagnosis or the low symptomatic severity was responsible
for the negative result in mD and ID. The most recent study using RDC criteria was conducted in GP settings by Lecriber et al. (1996) in MDD, mD and ID.

Venlafaxine was compared to imipramine and placebo prescribed for three months in 229 patients with mild to moderate depressions (Raskin score < 8). The improvement of the MADRS with venlafaxine was superior to imipramine from week 8. Both venlafaxine and imipramine were superior to placebo when considering the global rating by the physicians. However, like in the Paykel study only the most severely depressed (MADRS > 18) clearly benefited from the active compounds.

Overall, in spite of the existence of negative studies, it is clear that a substantial number of patients with minor chronic depression do benefit from drug treatment. MD and ID may be a too broad diagnostic category even more heterogeneous than dysthymia, therefore including subgroups of non-responders to drug treatment.

**DOUBLE BLIND COMPARISONS CONDUCTED IN PATIENTS WITH DYSTHYMIA**

The diagnostic criteria used in these studies are the definitions proposed by DSM-III (chronic mild depression) or DSM-III-r (excluding residual major depression with a more narrow definition of primary dysthymia).

Most studies show drug treatment to be effective in dysthymic patients when DSM criteria are used.

An exception is the study of Stewart et al. (1983, 1985). This group performed a six weeks double blind trial comparing desipramine and placebo in patients with major depression (MD) or dysthymia. Desipramine was significantly more effective than placebo in MD but not in dysthymic patients. Although this was a well conducted trial the number of dysthymic patients was low.

The results of the study by Tyrer et al. (1988) did not show impressive results for drug treatment in a group of 145 patients with various diagnosis including anxiety disorders. This study compared doxepin, diazepam, placebo, cognitive-behavioural therapy and self-help. In spite of the complexity of the design ending in small treatment-diagnosis subgroups the dysthymsics (65) responded better to doxepin than to diazepam or placebo. Kocsis et al. (1985) treated 76 patients with dysthymia in a double blind imipramine versus placebo controlled study. 55% responded to imipramine and 14% to placebo (HAM-D score < 7) after six weeks treatment. Phenelzine was also more effective than placebo in a study from Harrison et al. (1986). This was a six month duration trial following a good response to acute treatment in 12 dysthymsics. None of the 7 phenelzine treated patients relapsed but only one of the patients with placebo relapsed.

Different groups compared the efficacy of TCAs and MAOIs in dysthymic patients. Vallejo et al. (1987) compared phenelzine to imipramine in patients with MD and dysthymia.

Both drugs were effective in MD and dysthymia but phenelzine was superior to imipramine in dysthymic patients, a result similar to that of Quitkin et al. (1989). A new MAO inhibitor, moclobemide was compared to clomipramine in 191 patients with MD or dysthymia (35% of study sample) by Lecriber et al. (1995). Moclobemide is a reversible specific inhibitor of MAO. After 6 and 12 weeks treatment both drugs were found effective in patients with MD and dysthymia (2/3 responders for each diagnostic by treatment subgroup).
Promising results both at a practical and theoretical level are the findings with amisulpride in the treatment of dysthymic patients since it does not interfere with noradrenergic or serotonergic transmission like TCAs, MAOIs, SSRIs, or any of the drugs already mentioned. Amisulpride is a dopaminergic blocker with a high specificity for D2 and D3 dopaminergic receptors (Sokoloff et al., 1990) inducing a presynaptic blockade when used at low dosage (Scatton et al., 1994). After preliminary trials (Lecrubier et al., 1990) amisulpride was compared to imipramine and placebo for a six month trial in 219 dysthymic patients (Lecrubier et al., 1996). The improvement obtained with the two active drugs was superior to placebo after one month treatment and maintained after six months on the MADRS (main outcome criterion) and all other outcome measures. 88% of patients reported adverse events in the imipramine group, 53% in the amisulpride group and 60% in the placebo group. The response observed in the group of pure dysthymic (41% of sample) and in patients with double depression (dysthymia + MD episode: 59% of sample) was similar for both treatments. Another placebo controlled study from Boyer et al. (1992) compared amisulpride to aminphtiene in 323 dysthymic patients. The duration of treatment was 3 months and both drugs were found more effective than placebo on the MADRS scores and all other outcome measures.

A double blind comparison with fluoxetine, an SSRI, was presented by Smeraldi et al. (1996) in 268 dysthymic patients. After 3 month treatment no difference was found on the percentage of responders according to the MADRS (primary outcome criterion): 74% for amisulpride and 67% for fluoxetine. A significant difference in favour of amisulpride was found with the HAM-A. This result is consistent with the findings of Ravindran et al. (1994) suggesting that further studies are needed to explore the importance of anxiety in the therapeutic response of dysthymic patients to SSRIs.

Adverse events were more frequent in the fluoxetine group.

Interestingly when diagnostic criteria of DSM-III or -III-r for dysthymia are used for inclusion most double blind trials show reference compounds to be more effective than placebo. New drugs like moclobemide, amisulpride, aminphtiene and fluoxetine also appeared to be effective. When the study sample included a patient group with MD the results were rather similar with a non significant trend for MD to respond better but this may be due to a methodological bias since it is easier to show improvement with a higher baseline severity score.

A possible bias in the trials presented above is the high proportion of patients with double depression in the study sample, up to 96% in the study of Kocsis et al. In some studies it was possible to analyse the influence of the existence of a superimposed MD episode and results showed that pure dysthymics do benefit from pharmacotherapy. However, studies including specific samples without double depression are presented below.

**DOUBLE BLIND COMPARISONS CONDUCTED IN PURE DYSTHYMIC PATIENTS**

Versiani et al. (1994) compared imipramine, moclobemide and placebo in 315 primary dysthymics including a small proportion of double depression (one third of a sample). After 8 weeks treatment 60% of patients treated with active drugs no longer met criteria for dysthymia with active drugs compared to 21.6% in the placebo group. The percentage of improvement on the HAM-D for moclobemide, imipramine and placebo were 78%, 71% and 28% in the group of patients with double depression and 67%, 68% and 31% in patients with pure dysthymia. Another placebo controlled
Pharmacotherapy of Dysphymia

trial conducted in 416 pure dysthymsics also shows efficacy for the reference compound, imipramine and an SSRI, sertraline after 8 weeks treatment. Results of a one year follow-up will soon be available (Kocsis et al., 1994).

A further interest of this study is the low mean initial score close to 13 on the HAM-D, a score considered to discriminate between drug responders and non-responders by Paykel.

A study by Keller et al. (1995) comparing sertraline to imipramine found two third responders after 12 weeks treatment.

STABILITY OF REMISSION IN DYSTHYMIC RESPONDERS

Although dysthymia is by definition a chronic condition few studies were designed to assess the stability of response. Versiani (1996) treated 276 primary dysthymsics for 4 years with amitriptyline or tranylcypromine. The drop out rate was low (21.9%), the sample included 55% of pure dysthymsics (no current or past MD episode). All patients were responders to previous treatment (moclobemide, tranylcypromine or amitriptyline). After two years medication was stopped and an 89% relapse rate was observed. After reinstigation of treatment 80% of those who relapsed showed an improvement superior or equal to 70%. Kocsis et al. performed a 2 years follow-up in 123 dysthymic patients responding to imipramine or desipramine (10 weeks). 73 entered an open 16 week maintenance phase: 75% of patients remained stable on 13% improved (Kocsis et al., 1988a). Remitted patients after the 26 weeks period were randomised to desipramine or placebo for a maintenance phase of up to 2 years. 52% of patients relapsed under placebo and 11% on DMI (Kocsis et al., 1996). Among 12 patients who had a relapse during the 16 weeks maintenance phase 11 had a full remission when treatment was reinstored (Kocsis, 1995b).

These studies strongly suggest that maintenance therapy is necessary in dysthymic patients who responded to pharmacotherapy.

CONCLUSIONS

Contrarily to a common belief, dysthymic patients do respond to pharmacotherapy. Early double blind controlled studies had shown that patients with minor depression or intermittent depression according to RDC were benefiting from drug treatment.

More recently the trials including patients with dysthymia according to DSM-III or -III-r showed even more positive results against placebo. Reference drugs like imiprime, clomipramine and desipramine for TCAs, phenelzine and tranylcypromine for MAOIs were shown effective. New compounds as fluoxetine and sertraline (SSRIs) venlafaxine (serotonin and norepinephrine reuptake inhibitor), amisulpride (enhanced dopaminergic transmission) compared to reference drugs, exhibited the same order of efficacy.

Although patients with double depression were included in many trials those conducted in pure dysthymsics also found efficacy.

A large number of trials are now available showing a sustained efficacy for treatment durations superior or equal to six months.
No clear treatment of choice emerges from the literature as for efficacy. On the contrary, the
tolerance of new drugs like SSRIs, amisulpride or moclobemide was constantly found to be supe-
rior, this may be of importance if, as suggested by the available data, a long term maintenance
treatment is needed in these patients.

Few but well conducted trials strongly suggest that maintenance treatment is needed in dys-
thyemic patients. The relapse rates reported when stopping medication is at least equivalent to those
observed in major depression.

It is possible that the relatively poor long-term outcome described for dysthyemic patients may
be related to insufficient treatment or non compliance.

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