DYSTHYMIA IN
NEUROLOGICAL DISORDERS

DIVISION OF MENTAL HEALTH
AND PREVENTION OF SUBSTANCE ABUSE
WORLD HEALTH ORGANIZATION
GENEVA
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This document arises from a WHO meeting held in Geneva on 1-3 July 1996. It considers the definition of dysthymia in the presence of neurological disorders, the epidemiological information, some new data on molecular mechanisms and their role in the pathogenesis of dysthymia, as well as modern treatment approaches.

UNIT OF NEUROSCIENCE
DIVISION OF MENTAL HEALTH
AND PREVENTION OF SUBSTANCE ABUSE
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This document results from a WHO meeting on Dysthymia in Neurological Disorders, held at WHO, Geneva, 1-3 July 1996. The following experts participated:

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DYSTHYMIA IN
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1. INTRODUCTION

1.1 Welcome address

A WHO meeting on dysthymia in neurological disorders was held in Geneva on 1-3 July 1996. The meeting was opened by Dr. L. Prilipko, Chief of the Unit of Neuroscience, Division of Mental Health and Prevention of Substance Abuse who stressed the commitment of the World Health Organization towards the prevention, control, and treatment of neurological disorders as it is clearly indicated in the establishment of a Unit of Neuroscience.

2. SCOPE OF MEETING

Dr. Prilipko stressed the purposes of the meeting as follows:

2.1 To clarify the definition of dysthymia in the presence of neurological disorders.

2.2 To clarify the potential role of neuroendocrine mechanisms and dopaminergic systems in dysthymia in neurological disorders.

2.3 To evaluate the role of imaging of the brain methods in the assessment of dysthymia in neurological disorders.

2.4 To identify target molecular mechanisms that may underlie the symptoms of dysthymia in neurological disorders.

2.5 To discuss our present knowledge of dysthymia in specific neurological disorders.

2.6 To discuss current psychological and pharmacological treatments for dysthymia occurring in the context of neurological disorders.

3. DYSTHYMIA IN NEUROLOGICAL DISORDERS

3.1 Classification of dysthymia

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 these three factors. Therefore, the clinical manifestations and symptoms of chronic, mild depression lost relevance in face of the pathogenetic factors, and were considered just secondary or even masked by those factors.

DSM-III (American Psychiatric Association, 1980) changed this approach, and dysthymic disorder became part of mood (affective) disorders. The chronic character of
Dysthymic disorder has lead to some misunderstanding, and for many European psychiatrists, dysthymic disorder was a category corresponding more to depressive personality than to neurotic depression.

Mood disorders are the most difficult to classify of all psychiatric disorders. Reliability studies show in general lower kappa values for mood (affective disorders) than for most of other psychiatric disorders, excluding personality disorder and neurotic and anxiety disorders.

Co-morbidity of dysthymia raises very important questions. In a sense, co-morbidity is an artifact of modern nosology, which is based on symptoms. Epidemiological studies show a high overlap of diagnosis in mood disorders. Most patients with dysthymia may fulfill diagnostic criteria for other mood disorders, such as major depression (double depression). Furthermore, the diagnostic stability of dysthymia is poor. As a consequence, dysthymia has to be seen as one among several other mood disorders, including sub-syndromal forms, which may coincide at different moments in a single patient. Often, the fact of having a dysthymic disorder is a risk for developing major depression. In spite of all these difficulties, the concept of dysthymic disorder has been validated by epidemiological and clinical research and may be a useful one for the clinician who needs to classify in order to treat.

ICD-10 has a main difference from DSM-III/IV, namely that the limitations of function that a disorder in the social role (handicap) 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 disability is required for most of the psychiatric conditions.

Dysthymia shares in ICD-10 and DSM-IV a chronic evolution, specified in DSM-IV and in ICD-10 Research Criteria as two years of duration. The duration is not specified in the ICD-10 version for clinical purposes. It also shares the presence of a common set of symptoms (insomnia, low energy, fatigue, difficulty in concentrating, low self-esteem, loss of interest or pleasure and feelings of hopelessness).

The boundaries of dysthymia with major depressive episodes are different in ICD-10 and DSM-IV. This is due to the difficulties of finding appropriate cut-off points. The same applies for the frontiers with sub-syndromal conditions. ICD-10 uses a time criterium to separate dysthymic disorders 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. Dysthymia is not characterized by the presence of anxiety symptoms, but of long lasting anhedonia.
3.2 Dysthymia in the Western world

Epidemiological studies in the US and Europe have demonstrated that the point prevalence of dysthymia is at least 3% of the general population. Because of its chronic fluctuating nature, this disorder is among the most prevalent conditions encountered in general medical and psychiatric settings (Akiskal & Weise, 1992). 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 co-morbidity (20-35%) with such disorders as panic, social phobia, alcohol use, and eating disorders. A very common clinical presentation of dysthymia (50-80%) is double depression, which occurs when the low-grade dysthymic condition has been complicated by major depressive episodes. In view of the chronic - often lifelong - nature of dysthymia and the associated co-morbidity, 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. One of the most important studies in this respect is a prospective follow-up study of dysthymic children ages 6-9 years for up to age 18, demonstrating major affective (depressive or hypomanic) outcomes in up to 80% and anxiety disorders in 20%.

Another pattern of dysthymia - or low-grade sub acute 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. In one study, the common theme of these medical neurologic disorders was deficits in locomotion; e.g., rheumatologic, orthopedic, slowly progressive cerebral disease or arrested neurologic disease (such as history of poliomyelitis, encephalitis, stroke) (Akiskal et al., 1981). Other disorders include epilepsy, sleep apnea, and cardiovascular disease. In these dysthymia-like conditions occurring in the setting of medical-neurologic diseases, REM-density has been found abnormally decreased.

In the psychiatric literature the foregoing "secondary" cases of medical neurologic diseases 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 on 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 those observed in patients with such medical disorders as hypertension, diabetes, and cardiopulmonary disease. Dysthyminics 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 to neither 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 (Akiskal, 1983). As a result, physicians - including psychiatrists - often find it difficult to deal with these patients who might be labelled "existential depressives" or "depressive characters." Nonetheless, trait biologic findings - especially in circadian R.E.M. sleep parameters and TRH-TSH challenge tests - have been reported in primary dysthymia (Akiskal et al., 1980). 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. Not only have these trials shown response rates comparable to those in major affective disorders, but sleep deprivation has been reported to lead uplifting of the gloomy-lithargic disposition of these patients; some of these responses can even be described as transient hypomania.

In summary, 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 legitimate mood disorder (Akiskal, 1994; Akiskal, 1996). 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 sub-acute dysthymic forms encountered in the context of neurologic disease. The naturalistic outcome (of untreated) dysthymia is grave. Emerging data do suggest that it might also considerably aggravate the prognosis of co-existing medical and neurologic disorders.

3.3. Epidemiology of dysthymia in South America

There is very limited information on the epidemiology of mental disorders in South America. Variations in ethnic, demographic, socio-economic and cultural aspects preclude extrapolations from the scarce information available.

There are findings from two recent epidemiological studies carried out in Brazil. The first in 6470 adults of 3 large cities, used the QMPA (Almeida Filho et al., 1992). The second, which is still in progress, used the CIDI and they assessed mental disorders in catchment area of a large medical center in Sao Paulo (Andrade et al., in preparation). In the first study the prevalence of dysthymia ranged from 2.3% to 6.5% among the genders in the 3 centers. In the second, the overall prevalence was 2.9% (males) and 5.1% (females). Although these results are within the expected range, the latter data awaits confirmation from an ongoing SCAN/CIDI validation assessment. Their external validity, as mentioned, requires further study.

An additional aspect related to language barriers and geographic isolation of South American countries from the centers currently generating the concepts, training programmes and treatment plans for dysthymia is then addressed. This derives from problems with the concept of anxiety in depressive disorders (Lewis et al., 1979). Most Latin languages have two words for anxiety (e.g. "ansiedad" and angustia" in Spanish); one of them referring to feelings of pressure or constriction in the chest or in the throat, and more often associated with depression than with phobic-anxiety or panic disorders (Lopez-Ibor, 1950). The relationship of this with the prediction of therapeutic response in the early pharmacotherapy of depressive states is important in South America.
3.4 The neuroendocrinology of dysthymia and related affective disorders

Neuroendocrine abnormalities have been studied in affective disorders for several decades (Sachar et al., 1970). There are several reasons for the investigation of neuroendocrine function in mood disorders: 1) mood disorders are characterized by symptoms that reflect hypothalamic dysfunction: those include alterations in food intake, libido, and adrenal function; 2) levels of stress hormones are consistently abnormal in affective disorders; 3) stress can precipitate or worsen affective disorders; and 4) antidepressant drugs have an intrinsic effect on the levels of corticotropin-releasing hormone (CRH) gene expression.

In melancholic major depression it has been shown that there is marked hypercortisolism in the context of numerically normal adrenocorticotropic (ACTH) levels. Clinical neuroendocrine studies have demonstrated strong evidence for the following findings in melancholic major depression: 1) persistently elevated secretion of hypothalamic CRH; 2) levels of plasma ACTH that are numerically normal, but inappropriately high in the context of high ambient levels of cortisol; 3) high circulating cortisol levels; and 4) adrenal glands that respond to ACTH by hypersecreting cortisol (Gold et al., 1984; Gold et al., 1988a and b; Kling et al., 1994).

HPA function is now being defined in the other spectrum of affective disorders. Those are characterized by chronicity and symptoms of fatigue, anergy, weight gain, and rejection sensitivity, and include atypical depression, chronic fatigue syndrome, and some types of dysthymia. In those disorders it has been postulated that the marked anergy, fatigue, and chronicity are associated with a mild deficiency of the arousing producing neuropeptide, CRH. That hypothesis was derived from studies done on patients with Cushing’s disease, pre- and post-surgery. Those patients have low CRH levels and approximately 50% of them have atypical depressive symptoms (Dorn et al., 1995).

In order to test the hypothesis that low CRH levels might mediate the symptoms of dysthymia, several diagnostic categories, including chronic fatigue syndrome and dysthymia are being studied. The findings so far indicate that those patients have low ambient cortisol levels, blunted cortisol response to ACTH infusion, blunted ACTH response to ovine CRH (oCRH) infusion, and blunted ACTH response to arginine vasopressin (AVP) infusion. In conjunction, these findings are indicative of central adrenal insufficiency caused by low hypothalamic CRH levels (Demitrack et al., 1991).

In order to definitely confirm the presence of central adrenal insufficiency in dysthymia in general, or in dysthymia occurring in neurological disorders, new endocrine protocols have to be developed and validated, because the range between radioimmunoassay detection and normal values is very narrow. Thus, very sensitive methods have to be used to detect a pathophysiologically meaningful and statistically significant alteration in HPA activity in those patients. Methods that use either frequent sampling or deconvolution to assess neuroendocrine function should be applied to neuroendocrine studies in dysthymia. Frequent sampling permits the study of hormone pulsatility at the ultradian level. Deconvolution permits the assessment of instantaneous rates of hormone secretion, a
parameter that is far more precise than plasma hormone concentrations. The use of state-of-the-art specialized biophysical and mathematical techniques for evaluating in vivo hormone secretion by these approaches allows us now to conduct non-invasive reconstruction of the time domain of endogenous glandular secretory activity (Veldhuis & Johnson, 1990).

Other studies have shown evidence for endocrine dysfunction in patients with dysthymia, particularly those with early onset. Those abnormalities include alteration in HPA function as well as hypothyroidism (Sztodczky et al., 1994). Because thyroid abnormalities are frequently found in dysthymia and can be easily treated, every patient with dysthymia should have an evaluation of thyroid function.

The incidence of dysthymia is high: at a rate of 7% prevalence one can estimate that over 40 million individuals in the United States and Western Europe have had dysthymia. These numbers would be much higher if worldwide prevalence rates were determined. Dysthymia in the context of neurological disorders represent a new frontier in the endocrine neuroendocrine investigation. Gold et al. have hypothesized that dysthymia is associated with mild hypofunction of the HPA axis and decreased central production of the arousing producing peptide, CRH (Gold et al., 1995).

3.5 Molecular mechanisms of the stress response and their role in the pathogenesis of dysthymia

The response to stress is essential for survival. The organism requires for its existence a state of metabolic equilibrium or homeostasis. In order to survive, all living cells have developed biochemical and molecular mechanisms to cope with stress at the cellular, systemic, and behavioural levels. The most robust and reliable neuroendocrine finding in affective disorders is the dysregulation of the hypothalamic-pituitary-adrenal axis (HPA). A topical question in this field is whether there is a more causal relationship between stress-responsive neuroendocrine systems and affective disorders. Gold et al. (1984) have proposed 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.

In order to study the molecular substrate of the stress response and its relevance to dysthymia, recent work in this field has been focused on the expression of genes encoding stress-responsive neuropeptides, particularly the CRH system. That system is relevant for several specific reasons. It has been demonstrated through endocrine, post-mortem, and CSF data that CRH is elevated in depression. On the other hand, clinical studies have indicated that CRH is decreased in states characterized by symptoms of dysthymia.

CRH is a 41 aminoacid peptide neurohormone that is synthesized in the paraventricular nucleus of the hypothalamus (Vale, Spiess, Rivier & Rivier, 1981). CRH receptors have recently been cloned by Chen et al. (1993). A detailed localization study of CRH receptor type I gene expression in adult rat brain has found CRH receptor mRNA was observed over
the pituitary, and in areas that are important for the regulation of the HPA axis such as the hippocampus, PVN, ventromedial nucleus, and the arcuate nuclei of the hypothalamus.

A major effect of CRH receptor activation is to increase proopiomelanocortin (POMC) gene expression. A CRH-responsive element in the POMC promoter, PCRH-RE, has been recently identified (Jin et al., 1994) from CRH treated pituitary cells. The gene encoding the PCRH-RE binding protein 1 (PCRH-REB-1), a DNA binding protein that specifically binds to the PCRH-RE. PCRH-RE can increase transcription 5 to 7 fold. Studies examining the neuroanatomical identification of the sites of PCRH-REB-1 mRNA in adult rat brain showed that PCRH-REB-1 gene expression was present in several discreet areas in the brain, such as: cerebral cortex, hippocampus, amygdaloid complex, hypothalamic nuclei (PVN, supraoptic and arcuate) (Licinio, Bongiorno, Gold & Wong, 1995). The gene encoding for PCRH-REB-1 is localized in brain areas known to contain CRH or CRH receptors and which respond to CRH. This finding raises the possibility that PCRH-REB-1 gene expression may result from CRH action (Licinio et al., 1995).

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 these molecules should be useful 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. A marker of the cellular responsiveness to CRH should greatly facilitate future studies of 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 help clarify the biological basis of dysthymia.

3.6 The role of dopamine in dysthymia

A common feature of several depressive conditions (major depression; cyclothymic disorder; secondary depression; recurrent depressive disorders; minor depression; neuroasthenia; drug-induced depression and dysthymia) is the incapacity to experience pleasure and the lack of the energy needed to overcome stress or even to embark in daily routines.

The fact that most patients affected by this disorder can live all of their lives without feeling any pleasure, even if they come from different cultural, social, familiar and personal backgrounds, suggests that a common biological background might be present in all of them (Fibiger and Phillips, 1987)

Pre-clinical data suggest that in the above-mentioned clinical conditions a malfunction of the dopaminergic system (especially in its mesoaccumbens portion) may exist (Blackburn et al., 1992). Every time symptoms or signs (phenotype) of depression are modeled in experimental animals it is observed that the symptoms are sustained by a deficit in dopaminergic neurotransmission (Willner, 1983 a, b, and c). Those symptoms can be exacerbated by a blockade of dopaminergic receptors (Fourezios et al., 1978) or by lesions
of the dopaminergic pathways. The same symptoms can be prevented, ameliorated or even reversed by treatment with compounds that by different means (Gambarana et al., 1995) will increase dopamine neurotransmission (Serra et al., 1992).

Several models of depression might converge in producing a reduction of dopaminergic transmission by several mechanisms, giving support to the possibility of multifactorial etiology.

Interestingly, in the mild stress-induced model of depression, postsynaptic DA receptors are hyposensitive while dopamine release is normal. On the other hand, in the psychostimulant withdrawal model, postsynaptic dopamine receptors are hypersensitive whereas dopamine release is reduced. In both models however, antidepressant of several classes (TCA, SSRI etc) and non-pharmacological treatments (ECT, REM deprivation) will reverse the signs considered important in models of human symptoms of depression, suggesting that the reduction of dopamine transmission could be produced via different mechanism and giving support to the clinical observation showing distinct clinical entities.

The presence of hyper or hyposensitive postsynaptic dopamine receptors might explain the presence or absence of delusions, hallucinations, psychomotor retardation or agitation and the individual responses to treatment and the facility or resistance to switch from depression to mania. Several conditions may alter the ability of the limbic system to process reward related stimuli among these: stress, chronic emotional reaction, chronic sleep deprivation, use of psychostimulants, chronic antidepressant, withdrawal from various drugs, by altering the "normal" function of the dopaminergic system.

These observations also sustain the need of "individualizing" the diagnosis and the treatment of dysthymia (the need of proper clear-cut diagnostic criteria) that will take into account both the validity of such diagnostic criteria and also the personal history of each individual patient.

3.7 Cerebral blood flow in dysthymia

Available brain imaging techniques now make it possible to assess changes in regional cerebral activity with the unique opportunity to examine the pathophysiology of mood disorders. Studies conducted in the 80's often produced conflicting results. These initial discrepancies have emphasized the methodological issues that more recent studies strive to consider. Technical advances and more carefully planned clinical and therapeutical selection criteria now allow more consistent results.

As there is compelling evidence for a biological basis to major affective disorders, most of the studies conducted so far have focused on patients with primary major depression (D'haenen, 1992; Benco et al., 1993. Cumming et al., 1993; George et al., 1993). Only a minority of studies have examined patients with dysthymia or patients with secondary affective disorders.
A review of 50 studies on major affective disorders reveals interesting points that clinicians must address when considering the use of imaging techniques in dysthymia:

1. When compared to healthy controls, patients experiencing a major depressive state showed global and regional decrease in cerebral blood flow (CBF) or metabolism (CMR). In spite of widely distributed topographic modifications, the most common abnormalities observed included frontal, temporal, and less consistently other limbic CBF or CMR decreases.

2. Another common result is the asymmetry ratio with a right advantage during the depressive phase.

3. Correlative studies with clinical or cognitive features provide more contradictions; however, recent PET studies reported correlations between dorsolateral prefrontal cortex, decreased activity and psychomotor slowing. Some dimensional aspects of major depression like retardation, anxiety and cognitive impairment have been mapped by imaging methods.

4. Studies assessing patients in the depressed state and then during recovery, reported a reversal of some abnormalities, particularly in the frontal areas, suggesting that CBF or CMR decrease of those regions may be state markers. Changes in asymmetry with a decreasing of the right advantage, have also been described. These results suggest that frontal CBG or CMR decrease and/or changes in asymmetry may also be state markers related to major depression.

5. Four studies on dysthymia have been done. The latest publication was reported in 1993 (Thomas et al., 1993), and aimed to compare CBF of patients with major unipolar depression and double depressed patients (dysthymia with superimposed major depressive episode). Patients were found to have different rates of CBF, especially in the left frontal region. Patients with lower CBF had symptoms of major depression.

6. Receptor studies have been conducted only in primary or secondary major affective disorders with results that indicate new aspects about lateralization.

PET findings may be of interest to guide SPECT studies that would replicate and confront CBF or receptor binding results to a wider range of patients. SPECT is certainly not a diagnostic tool; however, it has the potential to assist in the differential diagnosis with dementia. SPECT might become a guide for therapy of patients by imaging impairment of brain functional organization as the therapeutic management progresses. The ability to determine predictive brain imaging pattern of treatment response may also be expected. The next generation of tools, particularly functional MRI, is expected to bring new advances to the study of dysthymia.
A useful recommendation on the use of brain imaging in research in dysthymia would be to encourage the utilization of standardized conditions of assessment to avoid discrepancies and isolated results.

3.8 Dysthymia in Alzheimer's and Parkinson's diseases

A careful review of dysthymia in Alzheimer’s disease (AD) and Parkinson’s disease (PD) indicates uncertainties about the onset of depressive disorder in relation to the neurological disorder, as well as evidence that dysthymic symptoms in AD and PD frequently have a duration of less than one year. These uncertainties have made the two-year duration criterion untenable for dysthymia in the neurological patient populations.

In every neurological disorder evidence has been found that there is a group of depressed patients who do not meet criteria for major depression. These sub-syndromal depressive disorders have also been called "minor depression" and have been differentiated from major depression both in AD and PD (Davous et al., 1995; Förstl et al., 1992).

In both AD and PD the duration of dysthymia is significantly shorter than the duration of major depression. In both AD and PD, dysthymic depression mostly occurs after the onset of the neurological disease, whereas about half of the patients with major depression start to suffer depressive symptoms before the onset of the neurological illness. However, while dysthymia is more prevalent in the mild stages of AD and PD, major depression occurs at all stages of these neurological conditions.

In PD, major depression was significantly associated with lower frontal hypometabolism and a faster decline in cognition and activities of daily living. On the other hand, dysthymia in PD is not associated with significant cognitive impairments and does not predict further declines in cognitive and physical functions. Thus, while major depression in PD may be related to biological factors, dysthymia in PD may represent an emotional reaction of predisposed individuals when confronted with the physical limitations of the disease.

Major depression in AD may also be related to biological factors, since it is significantly associated with both left temporo-parietal hypoperfusion and significantly hyper theta relative power in posterior brain areas of both hemispheres as compared to non-depressed AD patients. In contrast, dysthymia AD patients showed no biological differences as compared to non-depressed AD patients, and had a significantly better awareness about their cognitive impairments than AD patients with either major or no depression (Migliorelli et al., 1995).

Further research in this area should 1) validate the construct of dysthymia in neurological disorders; 2) examine the need to charge inclusion criteria for neurological patients; 3) determine the validity of present diagnostic constraints (e.g. duration criterion); 4) examine different treatment modalities for dysthymic patients with neurological conditions (e.g. pharmacotherapy vs psychotherapy, different types of antidepressant drugs); 5) propose specific diagnostic criteria for the different syndromes that are currently lumped together
under the concept of "organic brain syndrome"; and 6) start trans-cultural studies that will help to validate the concept of psychiatric disorders among patients with neurological illnesses.

3.9 Dysthymia in stroke

The prevalence of post-stroke dysthymic affective disorder, defined as affective disorder that meets DSM-III-R criteria for dysthymic disorder or DSM IV criteria for minor depression ranges from 40% (Eastwood et al., 1984) in hospitalized patients to 89% (Burvill et al., 1995) in community survey. The longitudinal course of these patients has been variable, with some showing chronic depression over two years that switches from dysthymia to major depression, while others show brief depression lasting only a month or two (Morris, Robinson & Raphael, 1990). There are numerous studies which have shown differences between major and dysthymic depression, including differences in severity of Hamilton depression scores and association with physical impairment (Bolla-Wilson et al., 1989). Dysthymic depression (dysthymia) is not associated with greater cognitive impairment compared to non-depressed stroke patients while patients with major depression show significantly greater cognitive impairment (Robinson et al., 1986). Clinical pathological studies found that major depression was associated with left frontal lesions while dysthymia was associated with right posterior lesions. Both major depression and dysthymic disorder were associated with increased mortality rate in both short-term (15 months) and long-term (10 years) follow-up (Morris et al., 1993). Finally, major depression can be effectively treated with nortriptyline (Lipsey et al., 1984). Dysthymia also improves significantly with treatment but preliminary evidence suggests that efficacy may be difficult to demonstrate because a number of dysthymic patients show a placebo-mediated remission of depression. These studies have provided evidence that dysthymia appears to be a condition which is distinct from post-stroke depression. They provide support for the validation of a second form of depression that is less severe than major depression in patients with stroke.

3.10 Dysthymia in multiple sclerosis (MS)

Symptoms of affective disorders are common in patients with MS (Schubert & Follart, 1993). In a study of 1,017 patients admitted in the 1988-1990, psychiatric consultation was requested for 258 patients (25.3%) (Cazzulo et al., 1983). Dysthymia was present in 10.5% of cases; major depression in 4.3%; bipolar disorder (different subtypes) in 8.2%. MS patients have a high incidence of dysthymia (10.5%), predominantly in the age range 25-35, and more frequently in females than in males (11.5 vs. 8.8). Dysthymia in the majority of cases becomes evident after the diagnosis of MS had been made. Dysthymia does not appear to be correlated with the degree of motor disability and it shows increased incidence with the increase of the duration of illness. Cognitive disturbances tend to be mild or absent. The type of clinical course of MS (relapsing-remitting vs. chronic progressive) does not seem to influence consistently the affective or cognitive features in MS patients (Beatty, 1993).
Despite the occurrence of 3% suicides reported in the literature of mood disorders in MS (Kahana et al., 1971) suicide has not been observed in other series although suicidal ideation can occur frequently (41.2%). Combined treatment with pharmacological agents and cognitive psychotherapy can achieve satisfactory results.

More attention ought to be paid to symptoms of dysthymia in MS patients; psychiatrists and neurologists may work together to treat those patients. Attention should also be paid to other affective disorders, such as depression. Family dynamics can contribute to distress and to affective symptoms in those patients and should be assessed.

3.11 Dysthymia in people with epilepsy

In its Greek origins, the term "dysthymia" means "ill humored" and can be traced back to the disruption of the melancholic temperament by Hippocrates. It is therefore of interest that the first description of a mood disorder, specifically depression and epilepsy were also attributed to Hippocrates. There have only been two documentations of dysthymia in the context of people with epilepsy (PWE). Mendez and colleagues (1986) compared 20 depressed PWE with 20 depressed individuals without epilepsy. The depressed PWE had more endogenous traits and a greater background of underlying chronic dysthymia: their response to medication was noted to be inconsistent. Thompson and colleagues (1992) compared 27 patients with psychogenic seizures and compared them to 22 epileptics - the patients with psychogenic seizures had more dysthymia.

Depression, on the other hand, is common in PWE. Approximately 20% of patients with temporal lobe epilepsy become significantly depressed and 62% of medically intractable complex partial seizures have significant past and present depression (Altshuler et al., 1980; Robertson et al., 1987; Robertson, 1988; Robertson, 1992; Robertson et al., 1994). It has been suggested that about 50% of epileptic patients become depressed.

Both adult and children PWE can become depressed and many studies based on both clinical judgment and using standardized rating scales support this statement. Controlled studies indicate that PWE have more depression than the general population, but few studies have compared them to patients with other chronic disorders.

The characteristics of depression in PWE suggest that most are non-endogenous (neurotic) of moderate severity and have high anxiety, anger and irritability. Many depressed PWE have had a past history of neurotic of depressive episodes, deliberate drug overdose and deliberate self-harm.

The etiology of the mood disorders in PWE is complex and multifactorial, and includes 1) genetic vulnerability, 2) gender (males may be proportionately more at risk), 3) psychosocial factors (such as stigma, life events) and neuroepilepsy variables. The latter includes complex partial seizures and temporal lobe epilepsy (especially left side), the duration of epilepsy (longer duration, more severe depression) and anti-epileptic drugs: both phenobarbitone and to a lesser extent vigabatrin have been implicated in depression in PWE.
The use of biological markers to identify depression in patients with epilepsy has received little attention. The only study conducted was that of Robertson & colleagues (1986) who indicated that the test was not useful in depressed people with epilepsy, due to both antiepileptic drugs and the fact that ACTH and cortisol secretion may be abnormal in PWE.

The treatment of the dysthymic or depressed PWE should be tailored to the individual and in all cases supportive psychotherapy is imperative. Thereafter, there should be rationalization of antiepileptic drug therapy (reduction of polytherapy, removal of phenobarbitone if possible, institution of monotherapy with carbamazepine if appropriate). Depending on the severity of the depression and provoking factors, cognitive-behavioural approaches, the prescription of antidepressants or even ECT may be appropriate. When considering antidepressants, it must be remembered that the majority of non-MAOI’s reduce the seizure threshold; there are antidepressant - anticonvulsant interactions and finally the efficacy of antidepressants in PWE has not been well investigated, with only two studies (Ojeman et al., 1983; Robertson & Trimble, 1985) having been conducted. It is suggested that there are "safer" antidepressants (which affect the seizure threshold less) such as the MAOI’s, butripyriline, doxepin, protriptyline, viloxazine and the four SSRT’s - fluoxetine, fluvoxamine, paroxetine and sertraline. Cure should be taken when using viloxazine as it may precipitate carbamazepine toxicity. Antidepressants which are not safe (as they may induce seizures more) include maprotiline, mianserin and chlorimipramine. When one prescribes antidepressants in PWE, one should use safer drugs, begin with small doses and increase the size of the dose slowly, and discontinue the antidepressant if there is an increase in seizures, with hospital admission advised if there is poor seizure control or the risk of status. The antiepileptic drug levels should be monitored regularly.

Finally, as suicide is increased in PWE (five times the general population and possibly as high as 25 times in the case of temporal lobe epilepsy), antidepressants which are safe in overdosage should be prescribed.

In conclusion, depressive symptomatology and major depressive disorder in epilepsy are common. Dysthymia per se in PWE has received scant attention in the literature. Thus, the true incidence, prevalence, phenomenology, and treatment of dysthymia in PWE are unknown quantities.

However, some of the depressed PWE in the many studies mentioned may have had dysthymia. Future studies (multicenter) are suggested to examine the prevalence, phenomenology, etiology and treatment of dysthymia in PWE.

3.12 Dysthymia and epilepsy in developing countries

Epilepsy is a major health problem in developing countries (Gureje, 1991). Several studies concerning the clinical aspects, therapeutic approaches and epidemiology have been conducted. In addition, sociocultural representations of epilepsy and its chronicity predispose to mood disorders, but few studies have been done in this area in Black Africans. For this reason, a prospective study examining dysthymia in epileptic black patients in Senegal was
conducted (Karfo, 1991). The study included 197 patients (126 men and 71 women). The age range was between 15 and 45 years. Cases of symptomatic epilepsy due to head trauma, stroke, viral, or bacterial or parasitic infection were excluded.

Dysthymia was diagnosed according to both the inclusion and exclusion criteria of DSM IV (American Psychiatric Association, 1980).

Of the 195 epileptics included in the study, 35 (17.76%) had dysthymia and 18 (8.25%) had cognitive impairment.

Neither gender, age nor socio-economic status were of etiologic significance in the dysthymia. All dysthymia patients had loss of energy, anorexia, insomnia and low self-esteem. Feelings of hopelessness and isolation were observed in twenty patients, while irritability was encountered in seven patients. Disproportionate or inappropriate guilt and suicide attempts were not observed.

Dysthymia was more frequent in focal epilepsy (53.37%) compared to primary generalized epilepsy (13.6%) and temporal lobe epilepsy (45.45%). The type of anti-epileptic drugs in this study did not play a role in the etiology of the dysthymia.

Dysthymia is not rare in epilepsy in developing countries. Further multicentered studies must be undertaken to evaluate its real frequency, phenomenology, etiology and treatment.

3.13 Dysthymia in children

In children, dysthymia often results in school performance and social interaction impairments. They are usually irritable and cranky as well as depressed, with low self-esteem, poor social skills and some pessimism.

The case definition of dysthymia in children was based on the DSM-III or DSM-R diagnostic criteria, the prevalence of dysthymia was higher in girls (1.4-7.9%) than in boys (0.8-1.5%) (Canals, 1995; Garrison, 1992). When children face stressful events such as sexual abuse, recovery from severe burns, or the Persian Gulf crisis, there is a statistical increase in the diagnosis of dysthymia. Family environment also plays an important role in the occurrence of dysthymia (Warner et al, 1995).

Compared to the major depression and double depression groups, more frequent externalizing disorders and more impaired social functioning are present in dysthymic children. Chronicity of dysthymia seems to be a determining factor in social functioning. Recently it has been found that childhood-onset dysthymic disorder may be an early sign of recurrent affective illness. For this reason, the interval between the onset of dysthymia and the first major depression may provide a window of opportunity for intervention and possible prevention of earlier episodes. Statistically significant improvements have been observed for the combination of several antidepressants, in comparison to placebo, beyond those seen with
either group of drug alone (Carlson et al., 1995). The short-term outcome in dysthymia in children is good (80.6%); however, there is a 35.7% probability of recurrence.

Child psychiatrists are interested in the biological basis of dysthymia in children. Some results suggest that high plasma dopamine-beta-hydroxylase, and hypothalamic-pituitary-adrenal (HPA) axis dysregulation may be related to dysthymia in children, and that children with dysthymic disorder have a lower rate of nonsuppression (29%) than children with major depression (69%) in the dexamethasone suppression test (DST) (De Bellis et al., 1984).

Further studies are needed to evaluate the incidence, prevalence, and social cost of dysthymia in children in various parts of the world.

### 3.14 Psychological treatment of dysthymia

There are several reasons why psychotherapy is often considered to be the treatment of choice in dysthymia. In dysthymia, the intensity of the depressive syndrome is rather low to moderate. In such cases, drug efficacy has been questioned, while on the other hand, psychotherapy has always been thought to be not working in severe but instead rather in the milder forms. Dysthymia is also a chronic disorder which has led to its conceptualization as a developmental, neurotic, and personality disorder as well as a risk factor for the development of secondary adaptation disorders. This can lead to the concept of psychosocial illness leading physicians and especially patients to seek psychosocial treatment.

There are several psychological theories trying to explain the development and course of depression. They can be summarized in an integrated model. Mood impairment, negative cognitions and expectations, a lack in social skills and coping behaviour, and stressors and social strain are inter-dependent phenomena which mutually exert negative influences on each other which can start a vicious cycle and foster the development of chronicity. This is true regardless of the original cause (Linden, 1996).

Psychotherapy can be targeted at each of these problem areas. Social skill training can improve coping and interpersonal behaviours. Problem-solving strategies can reduce chronic stress. Cognitive methods such as cognitive rehearsal or internal dialogue can change negative beliefs and expectations and also improve mood.

Psychotherapy requires specialized skills; certain confrontative approaches may not only be unhelpful, but may even intensify affective symptoms. Therefore, caregivers should be familiar with specialized approaches to dysthymic patients.

As chronicity is known to be a predictor of poor outcome, studies on acute episodes cannot easily be generalized to dysthymia. So far, for dysthymia there are only a few pilot trials on interpersonal and on cognitive psychotherapy (Markowitz, 1994). Results are promising and justify larger controlled outcome studies. These should also include drug treatment to allow the investigation of comparative efficacy and differential treatment indication.
In practice this means that psychotherapy of dysthymia is a treatment option which has its place in a sequential treatment decision process. In spite of the lack of sound empirical evidence for its effectiveness, it is a reasonable alternative if other treatment options are not available, feasible or contraindicated, or did not produce sufficient response. It could also be a choice if the patient is strongly inclined to psychological treatment.

3.15 Pharmacological treatment of dysthymia

Chronic minor depression was initially considered to be the consequence of a character neurosis and therefore not a target for a drug. An important conceptual change was introduced by DSM III when dysthymia was classified as an affective disorder. Akiskal (Akiskal et al., 1980) was among the first to claim that drug treatment was effective in a group of patients with chronic minor depression. Later on dysthymic patients were considered rather poor responders. This low drug efficacy was in addition used as an argument to separate dysthymia from major depression (Keller et al., 1982). In patients with chronic neurotic dysphoria, Rowan et al. (Rowan, Paykel & Parker, 1982) found no difference between phenelzine, amitriptyline and placebo. This lower response of minor depression to tricyclic antidepressants (TCAs) was true as well for MAOIs: Davidson et al. (1988) had better results in patients with major than in minor depression with isocarboxazid.

Various trials conducted in patients with dysthymia: TCAs were found effective in patients with DSM III criteria. Kocsis et al. (1988) found 55% responders (HamD < 7) for Imipramine and 14% for placebo. A new MAOI, moclobemide, has been found to be effective in double depression (67% responders) as well as clomipramine (70%). The corresponding figures for patients with "pure" dysthymia were 61% and 64% (Lecrubier et al., personal communication). Another new compound, venlafaxine, a selective inhibitor of both norepinephrine and serotonin uptake (Lecrubier, 1995) was compared in GP settings to imipramine and placebo in a 12 weeks trial. Venlafaxine was superior to placebo from week 8 to 12, the most sensitive criterion being the CGI rating by the GP. However, in these trials most patients reached the criteria for major depression in addition to dysthymia, therefore trials conducted in "pure" dysthymics were needed.

Studies conducted in patients with "pure" dysthymia were then reported. In 1994 Versiani reported a comparison of imipramine, moclobemide, and placebo in 315 primary dysthymic patients including a majority of double depressions. 60% of the patients that were treated with the active drugs no longer met criteria for dysthymia after 8 weeks of treatment compared to 21.6% of patients treated with placebo. Kocsis et al. (1994) reported the results of a large multicenter study conducted in 416 "pure" dysthymic patients; he evaluated the efficacy of a reference compound (Imipramine) an SSRI (Sertraline) compared to placebo. Both active compounds were superior to placebo even if the initial score of these patients was close to 13 on the HAM-D. A result in opposition with the findings by Paykel et al. (Paykel, Rowan, Parker & Bhat, 1982). However, Keller et al. confirmed this result in a sertraline versus imipramine double blind comparison (Keller et al., 1995).
Long-term trials in dysthymic patients were done as well. Preliminary trials had shown Amisulpride, a benzamide that enhances dopaminergic transmission when used at low doses (50 mg), to be effective in dysthymic patients. More recent studies compared 50 mg of Amisulpride to 100 mg Imipramine and placebo in a six-month double blind trial including more than 70 patients by group - based on the CGI 72% were responders with Amisulpride, 69% with Imipramine versus 33% with placebo. A similar study was conducted by Boyer et al. (1992) comparing Amisulpride to Aminexazine and placebo after a three-month treatment period. The results were similar. The stability of the response to tricyclics was assessed by Kocsis et al. in 73 responders to imipramine or desipramine (Keller et al., 1995). All of the patients were primary dysthymsics. After six months 89% of remitters still maintained their response, overall a high stability of the response was observed. Similar results are reported by Versiani et al. After a two-year maintenance treatment, 89% of patients who were discontinued Tranylcypromine or Amitriptyline relapsed.

In conclusion, not only reference drugs (TCAs or MAOIs) are effective in the treatment of dysthymia but new drugs with a better tolerance have also shown a relevant efficacy. SSRIs, moclobemide (a MAOI), Venlafaxine (inhibitor of norepinephrine and serotonin) and Amisulpride (Dopaminergic facilitation) all showed superiority to placebo and a response rate of two out of three patients. This response was shown to be stable. Therefore, a broad range of substances is effective in the treatment of dysthymia and the therapeutic choice between them is probably to be done more on tolerance than on efficacy. New antidepressants with a better tolerance and safety are indicated in chronic conditions to improve compliance. They also are devoided of cardiac toxicity and show a lower potential for seizures: this may be very relevant for the treatment of dysthymia with neurological disorders.

4. CONCLUSIONS AND RECOMMENDATIONS

4.1 Discussion

Classification of dysthymia in neurological disorders

The current classifications of dysthymia in ICD-10 in DSM-IV were discussed by all participants. There was particular emphasis on the definition of dysthymia in neurological disorders, both as a clinical concept and as a nosological entity. According to current classification, the diagnosis of dysthymia requires a duration of illness of at least two years. The participants felt that was too restrictive when there is co-morbidity with neurological disorders for three reasons. First, when occurring in the context of neurological disorders, there is clearly brain pathology that is already part of the diagnosis and that may contribute to the symptoms of dysthymia. Second, one of the reasons for the required two years for the clinical diagnosis is that this time requirement helps prevent a clinical diagnosis for those who might not have a "disease" that requires treatment and follow up. However, individuals with neurological disorders already have a medical diagnosis and require evaluation, treatment, and follow up for their primary neurological condition. Thus, an additional diagnosis of dysthymia should only facilitate the clinical understanding and treatment of those patients.
Finally, even though for some neurological disorders such as epilepsy, that are chronic and may not have defined gross brain pathology (e.g., tumor), the required time duration of two years might not be unreasonable, for other neurological disorders, such as stroke, that have abrupt and severe onset, it would be unreasonable to wait two years for the diagnosis of those patients. It was proposed that those patients could be diagnosed as having "minor depression" during the first two years of their disease, however the discussion by the group was that such a term was inappropriate as those patients’ syndrome is neither minor nor depression. Thus, the general conclusion was that in the context of neurological disorders, future editions of ICD and DSM should clarify whether the requirement that symptoms last two years before the diagnosis of dysthymia can be made is truly required. The longitudinal course of those patients should be further investigated.

Cultural aspects of dysthymia

The concepts of dysthymia, "angustía", "angoisse", "ansiedad", and anxiety were discussed. In most Latin language countries, two words, "angustía" or "angoisse" and "ansiedad" or "anxiety", define two different clinical states. The first is characterized by feelings of constriction or pressure in the chest and the throat and is more often associated with depression than with phobic-anxiety or panic disorders. The latter corresponds with anxious foreboding and tension, with autonomic symptoms. The use of one word in Anglo-Germanic languages precluded such distinction and is reflected in international classifications. It was discussed whether these aspects are relevant to dysthymia and would facilitate the understanding, evaluation, and treatment of dysthymia in neurological disorders in different cultures.

Dysthymia in Children

Dysthymia affects children with neurological disorders; however, the symptoms can be different from those that occur in adults. Symptoms seen in children include pessimism, hopelessness, lack of interest in playing, decreased enthusiasm for school, even though school performance itself may be satisfactory, and decreased social interactions with peers. Such symptoms should be carefully assessed so that an appropriate diagnosis can be made, leading to therapeutic interventions. Additionally, the clear identification of symptoms that are specific for children should lead to better outcome measures for this age group.

Neuroendocrinology of dysthymia

The clinical neuroendocrinology of affective disorders was reviewed. The findings in melancholic major depression were compared to those found in atypical depression and chronic fatigue syndrome. While melancholic major depression is characterized by hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, it is clear that in dysthymia there is decreased hypothalamic-pituitary-adrenal function. Current research strategies using deconvolution and assessment of instantaneous hormonal secretion rates, and rapid sampling for analysis of ultradian rhythms were discussed. Those methods should provide definitive data on the endocrine alterations occurring in dysthymia in neurological disorders.
Molecular mechanisms

The molecular mechanisms underlying the response to stress were discussed. Current research in this area is focused on corticotropin-releasing hormone (CRH), urocortin, CRH receptors, CRH-binding protein, and CRH responsive elements in target genes. The cloning and localization in brain of a novel transacting factor, proopiomelanocortin corticotropin-releasing hormone responsive element binding protein 1, PCRH-REB-1, offer a new tool for the study of the cellular responsiveness to stress. Finally, the identification of CRH responsive elements in viruses, oncogenes, and inflammatory mediators provides the possibility of a molecular link between chronic stress and the susceptibility not only to affective illness, but to medical and neurological disorders (Licinio et al., 1995). Chronic stress in neurological disorders might therefore have the potential to precipitate co-morbidity with dysthymia. The molecular mechanisms for these interactions are an active area of current research in molecular medicine.

The role of dopamine in dysthymia

The dopaminergic hypothesis of affective illness offers an explanation for the therapeutic effects of antidepressant drugs such as sulpiride and amisulpride that preferentially block DA autoreceptors and thereby increase DA output. Reduced neurotransmission in the mesolimbic DA system may sustain some of the core and subsidiary symptoms of dysthymia, namely anhedonia, lack of interest, lack of drive, lack of concentration, and psychomotor retardation.

Imaging studies in dysthymia

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

Dysthymia in specific neurological disorders

Few studies have been specifically designed to address the prevalence, correlates, and treatment of dysthymia in neurological disorders. Most studies among patients with neurological disorders included patients with either no affective symptoms, patients who met standardized criteria for major depression, and a separate group of patients with enough affective symptoms to meet the criteria for dysthymia, but who may not meet the two year duration criterion. The two years requirement to make the diagnosis of dysthymia in neurological disease can sometimes be a hindrance to the early characterization and treatment of symptoms that may significantly change the prognosis and outcome of the neurological disorder. To consider this condition a ‘minor depression’ may not be adequate, since these patients do suffer from a psychiatric condition that may have a negative impact upon the outcome of the neurological disorder, and which is susceptible to adequate treatment.
Affective disorders are highly prevalent in patients with neurological conditions such as epilepsy, stroke, Alzheimer's disease and Parkinson's disease. In both stroke and Parkinson's disease, several prospective studies demonstrated that the diagnosis of either major depression or dysthymia can worsen the outcome of these disorders, leading to a rapidly declining course of Parkinsonian patients and earlier death in post-stroke patients. Both major depression and dysthymia in neurological disorders may be successfully treated with antidepressant drugs. Whether antidepressant treatment may influence the longitudinal evolution of the neurological condition should be determined in future studies. Furthermore, specific prospective studies are needed to clarify whether the presence of dysthymia in other neurological disorders (e.g., traumatic brain injury, brain tumors, AIDS, etc.) may influence their outcome, and determine whether the use of pharmacotherapy to treat dysthymia may change mortality and morbidity in those disorders.

**Psychological Treatments**

It was discussed that there is no single psychotherapeutic approach to dysthymia. Specific psychotherapies should be employed, addressing issues such as cognition, mood, behaviour, and coping skills. Dysthymia can best benefit from specific treatments that optimize pharmacological approaches and specific psychotherapeutic approaches designed for dysthymia. The efficacy of various forms of psychotherapy in dysthymia needs to be examined by controlled clinical research studies.

**Pharmacological Treatments**

Dysthymia can be effectively treated pharmacologically. Not only reference drugs (TCAs and MAOIs) can be used, but new drugs with a better tolerability profile have also shown efficacy. The therapeutic choice among various antidepressants is probably more related to tolerance than to specific efficacy. However, it must be noted that very few controlled pharmacological trials have been conducted so far in neurological disorders. Thus, specific controlled treatment trials for dysthymia in neurological disorders are needed to evaluate the efficacy of pharmacological treatments.

### 4.2 Conclusions

There was a general consensus that dysthymia is important, but under-recognized and under-investigated in neurological disorders. Symptoms of dysthymia are clinically relevant in neurological disorders. However, some symptoms may be more relevant than those chosen in most rating scales in order to describe the symptomatic severity of dysthymia in neurological disorders. These symptoms are hopelessness, fearfulness, inability to cope with problems of daily living, and persistent pessimism. It was generally felt that at least in neurological disorders of abrupt onset and with a defined neuroanatomical basis, the diagnostic requirement of two years' duration is not clinically useful. Potential biological mechanisms for dysthymia include thyroid hypofunction, stress hormones and stress-related transcription factors, and reduced neurotransmission in the mesolimbic dopamine symptoms. In terms of specific neurological disorders it seems that dysthymia is an important element
in Parkinson’s disease, Alzheimer’s disease, stroke, multiple sclerosis, and epilepsy. Further clinical trials are necessary to clarify the etiology, biology, clinical manifestations and treatment of dysthymia in the various neurological disorders.

4.3 Recommendations

4.3.1 WHO should disseminate educational material on dysthymia in neurological disorders. It is clear that dysthymia is an important element in some major neurological disorders. Those include Parkinson’s disease, stroke, multiple sclerosis, epilepsy, and Alzheimer’s disease.

4.3.2 Neurological disorders are a heterogeneous group; further research in dysthymia should focus initially on neurological disorders where dysthymia may be clinically important and has been studied to date. Those disorders include stroke, Parkinson’s disease, Alzheimer’s disease, multiple sclerosis, and epilepsy. Affective symptoms have also been recognized in Huntington’s disease, Wilson’s disease, Gilles de la Tourette syndrome, headache, myasthenia gravis, head injury, and post neurological surgery, but there are no studies on dysthymia in those neurological disorders. It is recommended that dysthymia should be specifically studied in those diseases.

4.3.3 The definition of dysthymia in neurological disorders should be clarified. It was felt that the requirement that symptoms last two years before the diagnosis of dysthymia may be a potential problem in neurology, particularly in neurological conditions of abrupt onset such as stroke. It is recommended that current diagnostic criteria stating that the two years duration should be reexamined when dysthymia occurs in the context of neurological disorders.

4.3.4 A separate, specific WHO meeting devoted solely to address the concept and classification of dysthymia in neurological disorders is recommended.

4.3.5 Dysthymia and depression have distinct molecular genetic and neuroendocrine mechanisms. Further research is needed to clarify the specific neuroendocrine and molecular basis of dysthymia, and to help identify at the neuroendocrine and molecular levels markers that can differentiate dysthymia and depression.

4.3.6 As dysthymia has been under-investigated, prospective, clinical multi-center field research trials on the incidence, prevalence, biological mechanisms, follow-up, clinical impact, and treatment of dysthymia are necessary to better understand dysthymia occurring in the context of neurological disorders. The impact of dysthymia on the clinical outcome of neurological disorders should be assessed in those studies. Dysthymia may have a direct negative impact on neurological disorders; moreover, dysthymia may have a negative impact on compliance with treatment for neurological disorder. Therefore, it is recommended that future studies should assess the morbidity of dysthymia in neurological disorders.

4.3.7 Early treatment of dysthymia in neurological disorders should be seriously considered, as early therapeutic interventions seem to be highly beneficial.
5. REFERENCES


