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Dysthymia: clinical picture, extent of overlap with chronic fatigue syndrome, neuropharmacological considerations, and new therapeutic vistas

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Abstract

Dysthymia, as defined in the American Psychiatric Association and International Classification of Mental Disorders, refers to a prevalent form of subthreshold depressive pathology with gloominess, anhedonia, low drive and energy, low self-esteem and pessimistic outlook. Although comorbidity with panic, social phobic, and alcohol use disorders has been described, the most significant association is with major depressive episodes. Family history is loaded with affective, including bipolar, disorders. The latter finding explains why dysthymia, especially when onset is in childhood, can lead to hypomanic switches, both spontaneously and upon pharmacologic challenge in as many as 30%. Indeed, antidepressants from different classes — tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase A (RIMAs), selective serotonin-reuptake inhibitors (SSRIs) and, more recently, amisulpride, and spanning noradrenergic, serotonergic as well as dopaminergic mechanisms of action — have been shown to be effective against dysthymia in an average of 65% of cases. This is a promising development because social and characterologic disturbances so pervasive in dysthymia often, though not always, recede with continued pharmacotherapy beyond acute treatment. Despite symptomatic overlap of dysthymia with chronic fatigue syndrome — especially with respect to the cluster of symptoms consisting of low drive, lethargy, lassitude and poor concentration — neither the psychopathologic status, nor the pharmacologic response

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profile of the latter syndrome is presently understood. Chronic fatigue today is where dysthymia was two decades ago. We submit that the basic science — clinical paradigm that has proven so successful in dysthymia could, before too long, crack down the conundrum of chronic fatigue as well. At a more practical level, we raise the possibility that a subgroup within the chronic fatigue group represents a variant of dysthymia.

Keywords: Dysthymia; Neurasthenia; Chronic fatigue syndrome; Neuropharmacology

1. Introduction

Although the roots of what today we call dysthymic disorder (American Psychiatric Association, 1994) go back into nineteenth century continental European psychiatry (Brieger and Marneros, 1997), systematic research on the psychopathology and treatment of this disorder has been accomplished only during the past two decades (Akiskal et al., 1980; Akiskal and Cassano, 1997). This consensus statement summarizes current knowledge of this disorder and emerging data on its treatment.

Several documents have recently appeared on the clinical picture and advances in the pharmacotherapy of this disorder (Burton and Akiskal, 1990; WPA Dysthymia Working Party, 1995; Kocsis and Klein, 1995; Lecrubier and Smeraldi, 1996; Akiskal and Cassano, 1997). The present statement goes beyond these documents to address new developments on the relationship of dysthymia to other disorders within the affective spectrum, biochemical considerations of the rationale for the pharmacotherapy of dysthymia, including the possible relevance of the dopamine system to the core pathology of dysthymia; we also consider chronic fatigue syndrome and its treatment and whether it fits into the concept of an affective spectrum.

The term consensus as used herein does not necessarily imply that the authors of this document agreed on all fronts. We felt that the time was ripe and auspicious to delineate provocative links between basic neuropharmacology and clinical practice in the domain of dysthymia, but not to the exclusion of a discussion of discrepant findings in the literature.

2. Spectrum of subsyndromal, dysthymic, and major depressions

The core clinical manifestations of dysthymia consist of gloominess, anhedonia, low drive and energy, low self-confidence and pessimism (Akiskal, 1983b). As such, dysthymia differs from melancholia characterized by profound disturbances in psychomotor and vegetative functions. This is a familiar classical dichotomy in depression contrasting endogenous and neurotic depression. As opposed to the episodic full-syndromal course of endogenous depression, neurotic depression pursues a more fluctuating low-grade course (Akiskal et al., 1978). Until 1980, patients in the latter group were considered as suffering from a ‘character neurosis’. Because of the frequently chronic nature of their condition, their entire existence seemed immersed in melancholy, hence they were also often subsumed under the rubric of ‘existential depression’. The thesis that these chronic neurotic conditions represented subthreshold or subaffective expressions initially came from studies conducted at the University of Tennessee at Memphis (Akiskal et al., 1980), demonstrating sleep EEG findings, pharmacological response profile, and family history patterns similar to those of major affective disorders for a large proportion of these patients, justifying their inclusion as a form of mood disorder under the rubric of ‘dysthymia’ (= bad humor or mood). Many of these patients had insidious onset in late childhood, but developed major affective episodes postpubertally and in young adulthood (Kovacs et al., 1994). Such data further testified to the affective origin of dysthymic disorder.

Other studies have demonstrated the existence of a

pattern of chronicity that results from failure of recovery from major depressive disorders without antecedent dysthymia (Akiskal, 1982). In the NIMH Collaborative Depression Study (Keller et al., 1983), the joint pattern of dysthymic and major depressive disorders has been described as 'double-depressive'. Pharmacological studies (Stewart et al., 1988; Ravindran et al., 1995; Kocsis et al., 1997) demonstrating efficacy of various antidepressants for this spectrum of disorders have also revealed significant benefits in improving the social and interpersonal impairments which characterize these patients, further justifying the primary nature of the mood disturbance in dysthymia.

Related developments stemming from observations in US and Swiss epidemiological samples (Weissman et al., 1988; Angst et al., 1990), medical settings (Wells et al., 1989), and the inter-episodic phase of major depressive disorder (Judd et al., 1994), have demonstrated the existence of a prevalent group of less-than-dysthymic subthreshold depressions which have been dubbed 'minor,' or 'subsyndromal symptomatic.' Like dysthymia, these conditions are associated with impairment and are at risk for developing major depressive disorders during prospective observation. Briefer depressions of a few days' duration, which nonetheless recur at a severe symptom level, have also been more recently described (Angst et al., 1990) and appear to belong to a broad affective spectrum.

Genetic models (Kendler et al., 1992) that have explored the relationship between narrowly and broadly defined affective phenotypes suggest that the two lie on a continuum or spectrum. Comorbidity of dysthymia with such conditions as panic disorder, social phobia, alcohol abuse (just to name a few) is not uncommon (Markowitz et al., 1992; Akiskal, 1994). More often than not, dysthymia is chronologically the 'primary' disorder in such comorbid cases (Lewinsohn et al., 1991). Indeed, follow-up of low-grade depressive symptoms of dysthymia represent powerful prospective risk factors for major depression in adults (Broadhead et al., 1990; Horwath et al., 1992) and children (Kovacs et al., 1994). Finally, ongoing studies in San Diego (Judd et al., 1998) show that subsyndromal symptomatology of a dysthymic nature represents the modal lifetime condition of a patient with depressive illness.

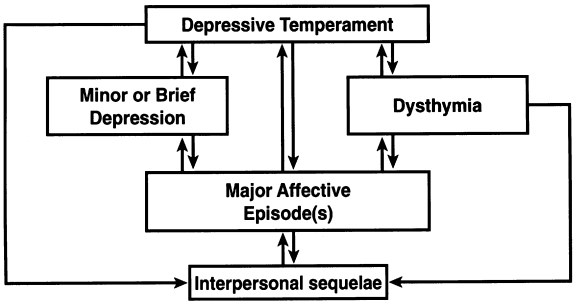

Fig. 1. Relationship of dysthymia to other affective spectrum conditions.

We lack the definitive studies regarding whether we are dealing with one or more spectra of disorders. What is clear is that the heterogeneity of depressive disorders can no longer be sub-classified on the basis of the severity of the clinical symptomatology. That is, depressive symptoms of varying severity seem to constitute the fluctuating life course of many depressive disorders, ranging from brief and subsyndromal to dysthymic and major episodic or visa versa (Akiskal, 1983a). This is shown in Fig. 1.

Dysthymia can thus pursue a course with a 'double depressive' pattern, fluctuating in and out of major depression, or pursue a relatively independent course of 'pure' dysthymia. The former constitutes two-thirds of dysthymias in psychiatric settings and the latter two-thirds of subjects in community and general medical settings (Weissman et al., 1988). Curiously, the ICD-10 (1992) concept of dysthymia is closer to community cases where superimposed major depression, if any, is mild and uncommon; DSM-IV (American Psychiatric Association, 1994), by contrast, liberally permits the 'double depressive' pattern of dysthymia fluctuating in and out of major depression. Both manuals agree, however, that low-grade depression woven into the habitual self of the patient represents the essence of dysthymia, whether or not major depressions supervene.

3. Relationship of dysthymia to the bipolar spectrum

Although both DSM-IV and ICD-10 specifically

preclude a diagnosis of dysthymia in cases comprising the occurrence of previous manic, mixed, hypomanic episodes or a cyclothymic disorder, systematic clinical observation, and family and prospective studies in adults and children have provided growing evidence of subtle links between dysthymia and bipolar spectrum disorders.

As early as 1978, a prospective follow-up study by Akiskal et al. demonstrated that 'neurotic depressives' developed major depressive episodes, half of which converted to bipolar II Akiskal et al., 1978. In their subsequent studies of a large cohort of chronic neurotic depressives, these authors postulated the existence of subaffective dysthymic disorders as chronic intermittent subsyndromal manifestations of primary major affective illness, many of which respond to antidepressants, and in selected cases, to lithium (Akiskal et al., 1980, 1981). Nearly a third of these subaffective patients were postulated to lie on a nosological continuum with soft bipolar disorders because of hypomanic switches on antidepressant pharmacotherapy as well as bipolar family history. Other clinical studies on 'neurotic', 'characterological' or 'masked depression' have also suggested a relationship between low-grade depressive pathology and bipolar spectrum disorders (Eastwood and Stiasny, 1978; Stone, 1978; Rihmer et al., 1983; Bronisch et al., 1985).

Findings on patterns of familial aggregation in the relatives of probands with dysthymia have shown high rates of mood disorders (Rosenthal et al., 1980; Angst and Wicki, 1990; Murphy and Checkly, 1990): a family history of bipolar disorder was reported in a higher percentage of patients with dysthymia than with unipolar major depression (Rosenthal et al., 1980; Kocsis et al., 1986; Klein et al., 1988).

In a sample of juvenile offspring or siblings of bipolar adults, Akiskal et al. (1985) showed a high percentage of subjects with an insidious intermittent onset classified as cyclothymic and dysthymic; during follow-up, some of the dysthymic patients developed bipolar II disorder. More recently, Klein et al. (1995) reported a higher rate of bipolar disorder among the relatives of dysthymic probands with a history of major depression compared to the relatives of normal controls.

The relationship between dysthymic conditions and bipolar spectrum disorders is further suggested by reports of brief hypomanic switches after antidepressant therapy (Rosenthal et al., 1980) or sleep deprivation (Rihmer, 1990), or even occurring spontaneously (Klein et al., 1988). In addition, the studies of Kovacs et al. (1984a), (1984b); Kovacs and Gastsonis (1989) on depressive disorders in childhood appear to substantiate the link between dysthymia and bipolar spectrum disorder. In children, dysthymic disorder was associated with a greater risk of developing major depression as well as bipolar disorder with hypomanic, manic or mixed episodes (Kovacs et al., 1994).

Cassano and Savino (1993), compared a group of dysthymics with a group of chronic major depressives on the basis of clinical and demographic characteristics, affective temperamental dysregulations, and first-degree family history. Dysthymic patients differed from major chronic depressives in showing an earlier age at onset and index age, subsyndromic features, a lower incidence of premorbid affective temperament, and similar rates of bipolar family history. These features were found to be closer to bipolar major depression than to unipolar depression, justifying the claim by Akiskal et al. (1980) that as many as a third of patients with dysthymia might belong to the bipolar spectrum.

The current controversies surrounding the nosologic status of dysthymia pertain to dimensional vs. categorical classification of depressions on the one hand, and the unipolar–bipolar dichotomy on the other (Akiskal, 1983b). Dysthymia reflects these controversies in that it represents a possible trait or dimensional (constitutionally-based) depression on the one hand, and a subsymptomatic depressive condition with links to soft bipolarity on the other. Akiskal et al. (1980) have gone so far as labeling the latter condition as 'sub-bipolar dysthymia'.

In summary, although a unipolar course is the most typical and prevalent expression of dysthymia, studies in clinical settings and cases of childhood onset do suggest that as many as a third of dysthymics might have links to the soft bipolar spectrum. This subtle link to bipolarity might explain in part why asthenia, lethargy and low drive characterize a subgroup of dysthymics (Akiskal et al., 1980). A factor-analytic Italian study (Serretti et al., in press) has likewise demonstrated the existence of

a dysthymic subgroup where chronic fatigue is the hallmark. These neurasthenic or 'deficit' symptoms in turn might be linked to a putative dopamine neurotransmitter pathology further elaborated in this paper.

4. Recent neurochemical considerations in depression

We now shift to putative biochemical considerations as pathophysiological bases for dysthymia and related illnesses. The pivotal role of biogenic amines (noradrenaline, dopamine and serotonin) in the mechanism of action of antidepressant agents (Brunello et al., 1994; Table 1) and the pathophysiology of depressive disorders was hypothesized nearly 30 years ago (Schildkraut, 1965; Bunney and Davis, 1965, Coppen, 1967). Since that time a large number of investigators have conducted studies on the biological mechanisms involved in the action of antidepressant agents and the information deriving from these studies has led to a number of revised and more refined theories on the biochemical abnormalities of mood disorders (Healy et al., 1983; Siever and Davis, 1985; Leonard, 1986; Stahl, 1996). Examination of Table 1 will reveal that putative neurotransmitter dysregulation involves not only the somatic features of depression, but also pertains to most of the emotional-cognitive disturbances occurring in dysthymic conditions.

Table 1
Correlation between depressive symptoms and monoaminergic systems involved in depression

	Noradrenaline	Serotonin	Dopamine
Vigilance	+ + +	+	+ +
Attention	+ + +	+ +	+ +
Cognitive functions	+ + +	+ + +	+ +
Mood	+ + +	+ + +	+
Affectivity	+ + +	+ + +	+
Psychomotor activities	+	+	+ + +
Pain	+	+ + +	+
Suicidal ideation	+	+ +	+
Avoidance	+	+ +	+ +
Impulsivity	+	+ + +	+
Aggressiveness	+	+ + +	+ + +
Anxiety	+ + +	+ + +	+
Sleep	+	+ + +	+ + +
Sexual functions	+	+ + +	+ + +
Appetite	+	+ + +	+ + +

The currently available antidepressants possess diverse chemical structures and apparently varying biochemical actions upon acute administration. All of these antidepressants take 2–3 weeks or longer before clinical improvement occurs, therefore recent studies on the mechanism of action of antidepressants have investigated the long- term effect of these compounds with respect to receptor changes and modification of intracellular events. On the other hand, the in vitro receptor affinity and the acute action of antidepressants better correlates with their side effect profile: TCAs lack specificity in their pharmacological action and are associated with antimuscarinic, antihistaminic and α-adrenergic blocking effects that account for many unwanted side effects; SSRIs have little or no affinity for the foregoing neurotransmitter receptors, with their most common side effect being related to $5HT_2$ stimulation (Cookson, 1993).

Research during the last 10–15 years has begun to provide a more complete understanding of the role played by second messengers and intracellular signal transduction pathways in those adaptive neural mechanisms that underlie behavioral phenomena relevant to depression and in the long-term effects of antidepressant pharmacotherapy. Thus, chronic administration of antidepressant drugs influences the density and function of noradrenergic (Banerjee et al., 1977), dopaminergic (Serra et al., 1992) and serotonergic receptors (Peroutka and Snyder, 1980) following persistent elevated levels of neurotransmitter. Such changes in receptors occur via adaptations of postreceptor signal transduction systems and regulation of gene expression. Since some of the same intracellular sites may subserve different receptors, intracellular adaptations could represent common postreceptor sites for antidepressant treatment that differentially affect these neurotransmitters acutely (Duman et al., 1994; Hyman and Nestler, 1996). Even if adaptations of beta-adrenergic, dopaminergic and serotonergic receptors per se may not underlie the therapeutic action of antidepressant agents, it is conceivable that adaptations of the cAMP intracellular signal transduction pathway, or of cellular proteins regulated by the cAMP pathway, are involved in the action of such. In fact it has

recently been reported that chronic administration of antidepressants alters the cAMP-dependent phosphorylation system (Perez et al., 1989, 1991; Racagni et al., 1992); this action could result in regulation of nuclear transcription factors thus influencing the expression of additional neuronal proteins (Nibuya et al., 1995). Other types of receptor regulation in response to chronic antidepressant treatment have been detected. Electrophysiological studies suggest in fact that the delayed onset of action of SSRIs is due to the time necessary for 5-HT_{1A} autoreceptors to desensitize, leading over time to an enhanced postsynaptic serotonergic neurotransmission (Blier and de Montigny, 1994).

Many adaptive modifications at receptor sites, beyond receptor level and in monoamine turnover have been reported after chronic antidepressant administration; however, the relevance of these changes in the mechanism of action of antidepressants and in the pathophysiology of depression is disputed by the lack of adequate animal models, by the uncertain ability to generalize experimental findings in laboratory animals to humans, by the inability to measure changes in monoamine synaptic activity in specific brain areas of patients and by the questionable relevance of biological markers in peripheral blood elements to neurons in the brain. The idea that biochemical abnormalities in the neuronal transduction mechanisms may underlie depressive psychopathology is further supported by new studies indicating that G-proteins and cAMP phosphorylation system may be altered in certain group of depressed patients (Schreiber et al., 1991; Manji et al., 1995; Perez et al., 1995).

In conclusion, the elucidation of intracellular signaling pathways and their effect on gene regulation has begun to provide a better understanding of the pathophysiology of depressive disorders. From the available clinical and preclinical data it thus appears that the future of antidepressant therapies may lie in the development of pharmaceutical agents which modulate signal transduction by acting on G-proteins or even at sites distal to the receptor-second messenger complex (Broekkamp et al., 1995). How these molecular events are linked to psychologically-defined stress and precarious adaptive mechanisms implicated in trait and state depressions is still a formidable challenge to psychobiology.

5. Does dopamine play a role in dysthymia?

New studies of the dopamine (DA) system — until recently the least favored putative substrate of depression — have given rise to plausible psychobiologic explanations. These studies (summarized by Fibiger, 1995) indirectly support the hypothesis that reduced neurotransmission in the mesolimbic dopamine system may sustain some of the symptoms of depressive conditions, including dysthymia. Experimental evidences indicate that mesolimbic DA plays a crucial role in controlling incentive motivation and reward. Finally, some antidepressants, irrespective of their acute action on the uptake of norepinephrine or serotonin, have the common property when given chronically to potentiate behavioral response to DA agonists. The DA hypothesis of depression (Gessa, 1996) offers an explanation for the antidepressive effect of pharmaceutical agents such as sulpiride and amisulpride given at low doses, that preferentially block DA autoreceptors and thereby increase DA output (Costa e Silva, 1990; Bocchetta et al., 1993).

It is well established that presynaptic autoreceptors in dopaminergic cells modulate the rate of firing (somatodendritic) and of transmitter release (terminal autoreceptors). In dopaminergic neurons of several species, including man, presynaptic autoreceptors are of the D_2/D_3 subtype (Mercuri et al., 1992). Selective blockade of DA presynaptic terminal autoreceptors produce an increase in neurotransmitter release.

Amisulpride is a selective D_2/D_3 antagonist which preferentially blocks the presynaptic dopamine autoreceptors which modulate the release of the transmitter through a negative feed-back mechanism. Thus, in vitro amisulpride enhances ^{3}H-dopamine release from brain slices during electrical stimulation. These nanomolar concentrations of amisulpride block the inhibitory effects of 7-OH-DPAT on ^{3}H-dopamine release elicited by electrical stimulation. Concentrations about 30 times higher are needed for blockade of postsynaptic receptors by amisulpride. The preferential blockade by amisulpride of presynaptic dopamine autoreceptors can also be demonstrated in vivo. Amisulpride increases dose-dependently the release of dopamine from the rat nucleus accumbens (dialysis in awake freely moving rats). These effects are obtained at 0.3, 1.0 and 3.0 mg/kg of amisulpride. On the other hand, doses of 10.0 and

30.0 mg/kg of amisulpride are required to antagonize the postsynaptic effects of apomorphine (apomorphine induced climbing). Thus, amisulpride is a selective and potent antagonist of presynaptic inhibitory DA receptors both in vitro and in vivo. The overall effect of low doses of amisulpride is to enhance dopaminergic neurotransmission (Guyon et al., 1993).

6. Rationale for the pharmacological treatment of dysthymia

Chronic depression for many decades was considered to be a milder form of depression, the consequence of a character neurosis and therefore to be treated primarily with psychotherapy (Arieti and Bemporad, 1978). However, evidence for the efficacy of psychotherapy as monotherapy for dysthymia is weak at best, if not disappointing (Weissman and Akiskal, 1984; Paykel, 1994; Markowitz, 1994). Although counter-intuitive, the evidence for the efficacy of pharmacotherapy in dysthymia is strong, and is documented below.

Systematic studies of pharmacotherapy in dysthymic conditions have paralleled the gradual evolution in our conceptual understanding of these forms of depression. This has resulted in a shift from viewing chronic depressions as personality or characterological conditions to their being better viewed as related to affective disorders. As summarized by Akiskal (1994), this conceptual shift is based on several lines of evidence along external validating strategies including family history, sleep EEG studies, positive response to sleep deprivation, as well as brief hypomanic switches upon pharmacotherapy; most importantly, both community and clinical studies have demonstrated progression of dysthymia to major depression.

Early therapeutic trials in chronic depressions had typically shown poor responses to TCAs, although these studies could now be criticized because of their lack of formal diagnostic criteria, inadequate medication doses, poor study design and poor outcome measures or criteria. Naturalistic studies also showed poor remission rates from chronic mild depressions compared to major depression. The results from these early studies suggested that milder forms of depression did not respond well to antidepressant treatment — with the possible exception of atypical depressions to MAOIs, as exemplified in the work of the Columbia group (Klein et al., 1980).

Akiskal et al. (1980), who found sleep EEG and familial evidence linking dysthymia to major depression, were the first to report in an open study that secondary amine TCAs (e.g. desipramine and nortriptyline) could be effective in a subgroup of dysthymics. It was based on a bold hypothesis supported by external validating strategies, and it went against the prevailing opinions of both psychoanalytic authors and biologic thinking of the day. Now, nearly 20 years later, the Pittsburgh group (Thase et al., 1997) has shown that depressed patients with abnormal sleep EEG are unlikely to respond to psychotherapy alone. This is reminiscent of the situation of dysthymic patients that Akiskal and colleagues described in 1980: the tricyclic-responsive dysthymics, who had abnormal sleep EEG, had failed to respond to past courses of long-term psychotherapy.

With the publication of DSM-III, dysthymia became more formally recognized as distinct clinical entities with specific diagnostic criteria. Both DSM-IV and ICD-10 have now officially sanctioned dysthymia. As a result, the need to find efficacious treatments for this prevalent and pervasive affective disorder became compelling. Clinical trials of patients with dysthymia (most of whom had double depression) found a positive response to TCAs, even among patients with mild symptoms (e.g., 8–13 Hamilton depression scores). Additional studies of double depression with MAOIs, including (phenelzine) and reversible agents (moclobemide), also found significant response rates comparable to TCAs and superior to placebo. More recent placebo controlled studies using moclobemide and imipramine in pure dysthymia have found significant drug–placebo differences, but no evidence for superior efficacy of a particular antidepressant (Versiani et al., 1997). This and other representative controlled studies of dysthymia are summarized in Table 2.

Another rationale for pharmacologic trials in dysthymia derived from basic and clinical research on so-called ‘deficit’ symptoms. Besides depressive symptoms, patients with dysthymia have been characterized by poor motivation, anhedonia, anergy, loss of activity and fatigue. These symptoms are similar to those described in animals with low or poor

Table 2
Representative controlled studies in dysthymia

Authors	Diagnosis	No. patients	Treatment	Improvement (%)
Vallejo et al., 1987	Dysthymia	32	Phenelzine	High doses of phenelzine
			Imipramine	better than imipramine
Kocsis and Francis, 1988	Dysthymia, early	75	Imipramine	45
	onset, moderate		Placebo	12
Lepine, 1992	Dysthymia	250	Toloxatone	70
			Fluoxetine	75
Guelfi et al., 1992	Dysthymia	164	Toloxatone	69
			Viloxazine	54
Hellerstein et al., 1993	Dysthymia	35	Fluoxetine	62.5
			Placebo	18.8
Versiani, 1994	Dysthymia	315	Moclobemide	67
			Imipramine	68
			Placebo	31
Thase et al., 1996	Dysthymia	416	Sertraline	59
			Imipramine	64
			Placebo	44
Lecrubier et al., 1997	Dysthymia	219	Amisulpride	72.2
			Imipramine	68.6
			Placebo	33.3

mesolimbic dopamine transmission (Gessa, 1996). For example, animals exposed to chronic mild stress have a generalized attenuation of response to reward, low psychomotor activity and poor motivation which can be reversed by chronic antidepressant treatment or by selective blockade of presynaptic D_2/D_3 autoreceptors that lead to enhanced dopamine transmission (Willner, 1995). This line of research is relevant to a putative neurochemical dimension that cuts across schizophrenic and certain depressive conditions. These considerations underlie the interest to use agents, such as amisulpride that enhance dopamine transmission by DA autoreceptor antagonism, as putative antidepressants in patients with dysthymia (Lecrubier and Boyer, 1995). Amisulpride, in low doses of 25–50 mg, selectively blocks dopamine autoreceptors, and is known to enhance dopamine transmission with reversal of anhedonia, amotivation, and poor response to reward. Clinical placebo-controlled studies of amisulpride compared to amineptine and to imipramine in dysthymia found that all active agents were significantly better than placebo. These results suggest that antidepressant agents that enhance dopamine transmission are effective in dysthymia and are comparable to the efficacy of standard antidepressants. This conclusion is upheld in a recently published large-scale double-blind Italian study (Smeraldi, 1998).

Interest in the pharmacotherapy of dysthymia has increased tremendously during the 1990s. The quality and variety of antidepressant treatment studies of dysthymia has also increased during this time. SSRIs, widely used in depression, represented a rational choice, such as the study by Hellerstein et al. (1993) with fluoxetine. A large number of placebo-controlled studies (a representative selection is summarized in Table 2) have shown that various antidepressants are effective in the acute treatment of dysthymia. Large-scale and rigorously designed placebo-controlled randomized study of the acute treatment of dysthymia found that sertraline and imipramine were significantly more effective than placebo and that sertraline was significantly better tolerated than imipramine (Kocsis et al., 1994; Thase et al., 1996). A much smaller number of studies have examined the post-acute continuation treatment of dysthymia (Kocsis et al., 1996; Versiani et al., 1997; Vanelle et al., 1997). The foregoing double blind and naturalistic studies cumulatively suggest that TCAs, Reversible Inhibitors of Monoamine Oxidase A

(RIMAs) and SSRIs are not only effective 'acutely,' but also in preventing the relapse of depressive symptoms in remitted dysthymics. This is a critical point, given the high risk of relapse in dysthymia.

Several interesting acute treatment studies of putative atypical antidepressants and related agents (i.e., tianeptine, amisulpride, flupenthixol and minaprine) have found them to be effective in dysthymia (Guelfi et al., 1989; Geisler et al., 1992). These agents tend to enhance serotonin and/or dopamine transmission, although their mechanism of action differ. The antidepressants bupropion and venlafaxine, which in addition to noradrenaline, also enhance serotonin and dopamine transmission, have not been studied in dysthymia in a prospective design. Venlafaxine in particular, has shown promise in the treatment of refractory depression (Nierenberg et al., 1994), including patients with chronic symptoms. Further research on the acute treatment of dysthymia with bupropion and venlafaxine are therefore warranted. In addition, such commonly used clinical strategies as lithium and thyroid augmentation for refractory depression have not been formally studied in treatment-resistant dysthymia; it is of interest that in their original open trial of antidepressants, Akiskal et al. (1980) used lithium on the grounds of positive family history in a third of dysthymic patients (Rosenthal et al., 1980).

Finally, combined pharmacotherapy–psychotherapy deserves systematic investigation in dysthymia. Although psychotherapy alone has not been found particularly effective in dysthymia, because of the chronicity of the disorder, combination therapy may confer some advantages over antidepressants alone. Both interpersonal and cognitive-behavioral approaches (Markowitz, 1994) deserve consideration in future studies that attempt to 'augment' pharmacotherapy.

7. The question of chronic fatigue syndrome

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis, chronic fatigue immunodeficiency syndrome or post-viral syndrome constitutes a major challenge for the clinician. Heir to the nineteenth century American concept of 'neurasthenia' (Beard, 1881), it was not formally defined until 1988 by the Centers for Disease Control (CDC, Holmes et al., 1988) and subsequently revised in 1994 (Fukuda et al., 1994; Wessely, 1994). Although chronic fatigue is common (Manu et al., 1992), CFS as defined by the CDC is less so, although still frequently found in primary care (Wessely, 1995).

CFS refers to patients with severe unexplained fatigue and exhaustion — both mental and physical — occurring after minimal effort, and accompanied by substantial disability (Fukuda et al., 1994).

The etiology of CFS remains uncertain. Some patients show immunological abnormalities, such as increased memory cells or low levels of natural killer cells, but these are inconsistent and non-specific. They are not related to clinical disability, and do not influence outcome (Swanink et al., 1996).

The role of viral infection is unclear, but has probably been overestimated. Several early studies suggested that the enterovirus family was implicated in CFS, but later investigations have not confirmed these findings (Swanink et al., 1994). In a large primary care cohort study we were unable to show any role for common viral infections as etiological factors (Wessely et al., 1995). Viral meningitis appears to be a risk factor for subsequent CFS, but probably more as a non-specific severe stressor than via a direct biological mechanism (Hotopf et al., 1996). Only Epstein Barr virus (EBV) appears to be associated with a direct post-infectious fatigue syndrome specific to that virus (White et al., 1995).

Most patients who fulfill criteria for CFS and are seen in specialist samples also fulfill criteria for psychiatric diagnoses, chiefly depression (David, 1991). Controlled studies have shown that these rates cannot be explained as a consequence of physical disability (Wessely and Powell, 1989; Katon et al., 1991). As similar associations are also found in primary care, selection bias is also not an explanation (McDonald et al., 1993; Wessely et al., 1996). Instead such overlap may be an inevitable consequence of the overlap between the diagnostic criteria for major depression and those for CFS.

Subjects identified with fatigue in the epidemiological catchment area (ECA) studies were between six and ten times more likely to fulfill criteria for dysthymia (Walker et al., 1993). Some authors who investigate chronic fatigue, particularly in Britain, use diagnostic systems that fail to recog-

nize dysthymia (Lane et al., 1991); even in the US it is 11% (Katon et al., 1991). In one of the few systematic follow up studies, the presence of dysthymia was associated with a worse outcome for fatigue (Bombardier and Buchwald, 1995). Dysthymia is possibly related to chronic fatigue rather than CFS.

Most studies and reviews on the subject of CFS and psychiatric disorder, have tended to emphasize the role of depressive rather than anxiety disorders. However, this is probably unjustified. Anxiety disorders are also common (Fischler et al., 1997), and current formulations of CFS emphasize the key role played by fearful cognitions in determining avoidance behavior and disability. The neurobiology may also show closer overlap with anxiety rather than depressive disorders. To emphasize depression at the expense of anxiety may reflect both the hierarchical nature of psychiatric disorder, the demise of the rich historical tradition of neurocirculatory asthenia, effort syndrome, Soldier's heart and their close associations with anxiety disorders (Paul, 1987; Fava et al., 1994), and the general shift of fashion and diagnostic preference from anxiety to depression (Young, 1989).

Despite these links, it would be an error to assume that CFS is simply a misdiagnosed psychiatric disorder. In every study between one third to one half of cases do not fulfill criteria for any psychiatric disorder (assuming one discounts neurasthenia as a diagnosis). Even within depressed cases, there are phenomenological differences between CFS and major depression. Some of these, such as relative absence of guilt and preservation of self esteem, might be explained on the basis of the external, as opposed to internal, attributions made by most CFS patients in specialist care (Powell et al., 1990).

Quite how one considers dysthymia and neurasthenia is unclear. Modern epidemiological studies are beginning to determine the prevalence of operationally defined neurasthenia: it is common in the community (Merikangas and Angst, 1994), and could be diagnosed in virtually everyone who attends a specialist CFS clinic (Farmer et al., 1995). Rather than attempting more fine-tuned distinctions between CFS, neurasthenia and dysthymia, a population perspective is likely to conclude that all three lie in dimensional space on an axis somewhere between anxiety and depression (Goldberg and Huxley, 1992).

Interest in possible hypothalamus–pituitary axis (HPA) abnormalities in CFS was generated by the similarities between symptoms in Addison's disease (primary adrenal insufficiency) and CFS. Demitrack et al. (1991) showed that CFS patients had a low evening plasma cortisol level, and decreased 24-h urinary free cortisol output, suggestive of mild hypocortisolism. Pituitary responsiveness to CRH was reduced, while the adrenal cortices were hyperresponsive to low doses of administered ACTH. However, at higher doses the adrenal cortisol response was impaired. This was interpreted as evidence of mild hypocortisolism of central origin.

Cortisol is closely related to central 5-HT systems; stress induced CRH secretion is partially controlled by 5-HT_{1A} neurones projecting to the hypothalamus (McEwen, 1995). In a recent study central 5-HT function was assessed in CFS patients without comorbid depression by measuring the prolactin response to D-fenfluramine (Cleare et al., 1995): CFS patients showed higher 5-HT mediated responses than controls, with lower circulating cortisol levels. Depressed patients showed the opposite. Increased central 5-HT responsiveness was also found in a previous study (Bakheit et al., 1992). The explanation of these observations is not straightforward. It may be that they reflect the observed differences between CFS patients, characterized by hypersomnia, appetite gain and fatigue, and classic major depression, with insomnia, anorexia and agitation; it is also possible the neuroendocrine changes are simply epiphenomena of these functional differences (Leese et al., 1996). The similarity between the preliminary neuroendocrine profiles found in CFS and those observed in disorders closer to anxiety than depression, such as post-traumatic stress disorder, is also intriguing (Yehuda et al., 1991). One formulation of disability places greater emphasis on the role of exercise avoidance, fear and conditioned responses rather than simple mood disorder, suggesting that depression per se may be an inadequate explanation of CFS. This conceptualization also suggests that CFS (in the absence of depression) lies at one end of a spectrum of HPA activity, in which major depression is found at the other.

Several magnetic resonance imaging (MRI)

studies of CFS have been published (Cope and David, 1996). Cerebral white matter abnormalities have been reported in some, but not all. (Cope et al., 1995). Functional neuroimaging techniques such as SPECT in CFS have generated inconsistent results. The most widely publicized study found that brainstem perfusion was significantly reduced in CFS subjects compared to controls, with depressed patients showing intermediate values (Costa et al., 1995). This study requires independent replication (Cope and David, 1996).

To summarize the literature thus far reviewed, the pathogenesis of CFS is unknown. Several reports stressed viral causes or immune dysfunction implying either the central nervous system or a neuro–muscular impairment. However, no findings have been consistently replicated. No biological marker or reliable test has been validated and the diagnosis still relies on clinical case definition.

Given the somatic emphasis in the etiology of CFS, many compounds such as antiviral agents, immune modifiers, vitamins, minerals, essential fatty acids etc. have been reported anecdotally or in open trial to be effective. However, no therapy has been demonstrated to be reproducibly useful in double-blind, placebo-controlled clinical trials with an adequate duration of follow-up (Blondel et al., 1993). In particular, replication and controlled studies are needed for most therapies with claimed efficacy such as carnitine, magnesium supplements, high dose essential fatty acid supplements etc.

CFS is frequently associated with depression, especially dysthymic-type low-grade symptoms. However, the observed response to antidepressants in CFS is insufficient by itself to support the position that CFS is just a variant of major depression. One possible logical conclusion to date is that CFS may share some overlap of symptoms and neurochemical mechanisms with major depression (Goodnick and Sandoval, 1993).

The association between CFS and depression led to open trials with antidepressants in these disorders. There are several reports of clinical benefits from antidepressants on CFS (Behan et al., 1994; Goodnick et al., 1992), but there is no published positive controlled trial yet. The first randomized, double-blind, placebo- controlled study of fluoxetine in CFS was resoundingly negative (Vercoulen et al., 1996). A double-blind, placebo-controlled trial of fluoxetine and a graded exercise program for CFS has been conducted (Wearden et al., 1998), showing a significant treatment effect, either with fluoxetine or exercise. Fluoxetine was associated with a significant change in fatigue scale scores as well as on anxiety and depression measures; however, there was no change on functional work capacity.

Oxford researchers (Wessely et al., 1991; Surawy et al., 1995; Sharpe, 1996) have suggested a heuristic model for understanding chronic fatigue syndrome which provides a psychotherapeutic rationale. At the heart is the message that whatever triggers CFS may not perpetuate it. For example, an ordinary viral infection may precipitate fatigue which, for the majority of the population, is resolved when a normal recovery is made. However, on rare occasions the presence of perpetuating factors (such as psychosocial stressors, rapid deconditioning, failure to rest adequately or concurrent depression) may delay or impede recovery. Fatigue then becomes chronic, persisting long after the departure of the original trigger and maintained by new variables. This would suggest the potential utility of cognitive-behavioral approaches, as is beginning to be confirmed by early trials.

8. Conclusions

Dysthymia refers to low grade intermittent, typically chronic, possibly constitutionally-based affective pathology characterized by gloominess, anhedonia, low drive and energy, low confidence and pessimistic outlook (Akiskal, 1996). Such patients, constituting 3–6% of the community, are quite prevalent in general medical settings where they present with unexplained physical symptoms (especially low energy) and psychiatric settings where they present with complaints related to an anhedonic life-style or its complications (including interpersonal and occupational disturbances and sometimes suicidal ideation or attempts). Long-considered characterologic in origin, recent data suggest that this disorder represents a variant in the course of primary affective illness in as much as many purse a double depressive course (dysthymia plus major depression) or a pure dysthymic course. In many cases, especial-

ly those with childhood onset, brief hypomanic switches do occur either spontaneously or upon antidepressant challenge.

Although traditionally the domain of long-term psychotherapy and psychoanalysis, psychotherapy — even in its most practical cognitive-behavioral and interpersonal forms — has not been shown to be effective in monotherapy. By contrast, most classes of antidepressants (including TCAs, MAOIs, RIMAs, SSRIs as well as atypical antidepressants and amisulpride) have been shown in double blind studies to be effective against placebo in an average of 65% of dysthymic patients. Naturalistic as well as double-blind long term extension of several of these studies over 2 years and even beyond (Akiskal, 1993; Kocsis et al., 1996; Versiani et al., 1997) have shown continued benefit from several of these agents. We need new studies to determine whether cognitive-behavior and interpersonal psychotherapies can enhance the benefit of long-term pharmacotherapy. New pharmacotherapies with either more specific neurotransmitter action or favorable profile of side-effects (e.g. SSRI, RIMA and amisulpride) have considerably facilitated the long-term clinical management of dysthymic patients.

In this consensus statement we have also considered new biochemical developments which may provide a putative pathophysiologic substrate for selected aspects of the dysthymic pathology, especially low drive, anhedonic-anergic manifestations. Whether some patients with 'chronic fatigue' belong to this category of patients is presently unknown. What is clear is that many patients with dysthymic-type pathology (including low energy and fatigue not necessarily meeting the stringent criteria for 'chronic fatigue syndrome') do present to general practitioners and psychiatrists. New, more specific pharmacologic treatments, possibly combined with new psychotherapeutic approaches, have provided new hope for this group of patients previously deemed recalcitrant to treatment. This hope is presently closer to practice reality in the clinical management of dysthymia. We have considered CFS, not because we believe it is isomorphic with the concept of dysthymia, but to underscore our conviction that the basic science–clinical practice paradigm that has been so successful in dysthymia could be equally fruitful in the conundrum of chronic fatigue.

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