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Proposed endophenotypes of dysthymia: evolutionary, clinical and pharmacogenomic considerations

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Dysthymia is highly prevalent—though underdiagnosed—occurring in at least 3% of the population. We conceptualize it as the clinical extension of adaptive traits that have developed during evolution to cope with stress and failure. A classification of dysthymias into anxious and anergic subtypes—and their putative association to bipolarity—is proposed. We further posit neurochemical and neurophysiological substrates for the two subtypes. A better recognition and understanding of dysthymic subtypes and their respective place in the affective spectrum will increase the proportion of people that may benefit from targeted treatments. It would also expand the pool of subjects that may be enrolled in genetic and pharmacogenomic research studies. *Molecular Psychiatry* (2001) **6,** 363–366.

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Dysthymia: adaptive and maladaptive

Adapting mood to changing external and internal environment is a plausible underlying rationale for the persistence of affective traits in the population.[1,2] Dysthymia, the best studied of the chronic subthreshold affective conditions,[2] involves at least 3% of the general population.[3] It is characterized by fluctuating low drive, low energy, low self-esteem and low hedonic capacity.[4,5] It appears in continuum with the more prevalent normal variations in affective temperaments, which account for 20% or more of the general population at large.[2,6–8]

As an adaptive mechanism, milder degrees of dysthymia might serve the purpose of making people desist and retreat in the face of ongoing *stress* (such as an overwhelming hostile environment), or *failure*. As a maladaptive condition, dysthymia clinically manifests by retreat from routine daily activities instead of coping head-on with them. Dysthymic traits may have been evolutionarily advantageous over time in certain sub-populations and environments, and thus selected for.[2,9] Gender differences—female dominance[3]—in dysthymia and depression may also have an evolutionary rationale.[10]

A tale of two dysthymias: anxious *vs* anergic

Dysthymia waxes and wanes in a person's life history, and is associated with a variety of 'co-morbid' conditions—the main ones being anxiety disorders.[11,12] We would therefore propose to classify dysthymia into two groups: dysthymia with anxiety, which we would term 'anxious dysthymia' *vs* dysthymia without anxiety, which we would term 'anergic dysthymia.' This dual conceptualization has its roots in previous work by us and others.[4,13,14] As explored in this paper, the two types of dysthymias may have different pharmacological responses, with different putative underlying biological mechanisms. Previous similar (but not necessarily overlapping) terms used were 'atypical' *vs* 'typical.'[14] Terminology in this relatively new field is not yet standardized, which could lead to confusion. Our proposed terminology is more descriptive and hopefully more accurate than the formal category of dysthymic disorder in US and International systems of classification.

Anxious dysthymia

Anxious dysthymia is characterized by insecurity and low self-esteem. The person may exhibit restlessness, but with lack of efficient, directed activity. A hyperactivation of the corticotropin-releasing-hormone, or CRH, system, and the locus ceruleus-norepinephrine, or LC-NE system, may be involved.[14] Anatomically, their amygdala may be enlarged and more metabolically active.[15] Its exacerbation is often a response to perceived ongoing *stress*. There may be a history of past loss or other trauma that may have sensitized the person to future stress,[16,17] hence its possible affinity to the realm of post-traumatic stress. Such individuals may be impulsive, have interpersonal rejection sensitivity,[2,18] and commit perhaps more frequent and dramatic, but not necessarily lethal, suicide attempts. They tend to ask for help, in direct or indirect ways.

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They may be labeled on axis II cluster B or C.[19,20] Their sleep is unsatisfactory, with frequent arousals.[13] Clinical experience suggests that such individuals often use sex as a way to obtain reassurance and solace, while some resort to other activities with 'reward' potential, like shopping and gambling.

Anxious dysthymia is more common in women.[21] It responds well to SSRIs,[12,22] and is likely due in part to suboptimal serotoninergic function. A subset of patients may discover and self-medicate with anxiolytic drugs of abuse like benzodiazepines, marijuana, opiates, alcohol, or more mundanely with food.[12] They engage in bulimic behavior and/or gain weight.[23] Women may be more susceptible to this aspect than men due to their baseline resistance to leptin, a hormone that regulates satiety.[24] Long-term maintenance therapy with SSRIs is often needed, and provides these patients with emotional dampening in the face of daily stressors.[12] High doses of antidepressants may, however, paradoxically worsen their underlying state of anxious brooding and agitation into a mixed state, and a mood stabilizer may be required at that point.[12] Some of these patients, over time, exhibit a bipolar II transformation.[12,25]

Anergic dysthymia

Anergic dysthymia is characterized by sluggish reactivity, low drive, low energy, and anhedonia: they exhibit psychomotor inertia. Dysthymics with such features may be characterized by reduced activity of the hypothalamic-pituitary-adrenal axis,[14] and in this respect can be said to have similarities to 'chronic fatigue syndrome'[26] (possibly a modern version of the classical 'neurasthenia'). Anergic dysthymia can be conceptualized as a response to perceived massive *failure*. These people are less impulsive, but exhibit more distorted thinking and may commit less frequent but more serious, fatal suicide acts.[27] They tend not to ask for help. It may appear to the observer as someone with negative or deficit symptoms.[28,29] They may be labeled on axis II cluster A or C.[19,30] They often exhibit hypersomnia and decreased REM latency,[13] as well as a decreased interest in sex.[30] They also have decreased appetite, and may lose weight.[12] It may be more frequent in men.[30] It may best respond to dopaminergic and noradrenergic boosting medications, eg, buproprion, venlafaxine, amisulpiride, stimulants, or older antidepressants like the tricyclics.[5,6] It is likely due at least in part to a dopamine deficiency,[31] and boosting dopamine pharmacologically may lift them out of their doldrums.

A subset of them may discover and self-medicate with stimulant drugs of abuse, like metamphetamine, cocaine, or more mundanely nicotine and caffeine.[30] Some of these patients tend to exhibit over time more of a bipolar I denouement, that being especially the case in those with childhood onset dysthymia.[32] Mood stabilizers should then be the mainstay for long-term therapy. If and when they swing from a low dopamine state to the high dopamine state, dopamine blocking neuroleptics in small doses may be needed for acute stabilization. Amisulpride, which in low doses boosts dopamine and in higher doses blocks dopamine, may be a particularly suitable pharmacological agent for such patients.[33]

Concluding remarks

In our increasingly fast-paced and time-compressed society, individuals with depressive traits may have difficulty adapting and evolve into a protracted clinical state of dysthymia. Psychological coping is compromised,[34] and the same appears to be true for immune parameters.[35,36] Dysthymias presenting clinically are often associated with more severe mood states,[12,37–39] influence quality of life,[40] morbidity and mortality,[41,42] and need to be treated more vigorously.[12,43,44]

A subset of dysthymias, anxious dysthymias, may exacerbate in response to perceived stress, and are hypothetically subserved by low serotonin:[34,39] serotonin is a powerful regulator of mood, calmness and composure in terms of dealing with stressful events. Another subset of dysthymias, anergic dysthymias, may exacerbate in response to perceived failure, and are hypothetically subserved by low dopamine:[31] dopamine is part of the reward mechanism that was shaped by evolution to reinforce success. It is the engine providing motivation and drive to both motor and thinking activities. Table 1 contrasts the two dysthymias.

Correctly identifying these subsets of dysthymic individuals permits us even now to target our treatment to the underlying biology and thus decrease the number of attempts at different pharmacological agents until a good response is achieved. Moreover, for the future, we submit that this proposal to classify dysthymia into two distinct endophenotypes, anergic and anxious, while undoubtedly oversimplistic, has heuristic value, especially in terms of aiding psychiatric genetics, clinical trials and pharmacogenomic research (Figure 1).

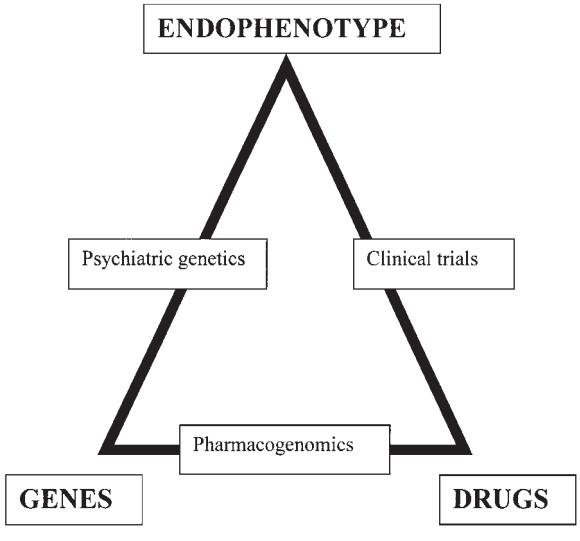

Figure 1 Proposed relationship between endophenotypes, genes and drug discovery.

Table 1 Putative dysthymic endophenotypes

Dysthymia	*Anxious*	*Anergic*
Anxiety co-morbidity (definitional)	yes	no
Precipitant/exacerbant	perceived stress	perceived failure
Antidepressant	SSRI	non-SSRI
Bipolar co-morbidity	II > I	I > II
Mood stabilizer	anticonvulsants	lithium
Psychosis co-morbidity	positive symptoms	negative symptoms
Antipsychotic	?	? atypical
Suicide prodromes/completion	high/low	low/high
Gender distribution	F > M	M > F
Sleep changes	? increased REM latency	decreased REM latency
Endocrinological changes	high CRH and LC-NE leptin resistance	low CRH and LC-NE ?normal/increased leptin response
Anatomical changes	? enlarged amygdala	?
Underlying biochemistry	low serotonin	low dopamine

Affective states defined by underlying long-term dysthymia have higher familial loading for both unipolar and bipolar disorders compared with that of 'pure' or episodic major depressive states.[12,25] Although conventionally, in our official nomenclature, bipolarity is excluded in the setting of a dysthymic disorder, follow-up studies do support the development of pharmacologic hypomania and even spontaneous mania in the course of dysthymia.[6,12,25,32] Such considerations suggest the need for a more complex conceptualization of dysthymia within the affective spectrum that extends, to some extent, into the bipolar spectrum. It is likely that distinct, if overlapping, sets of genes are involved in the two dysthymic subtypes proposed, some being susceptibility genes, and others being protective genes.[45,46] In order to identify them through convergent functional genomic approaches,[45] we need improved and more clearly defined endophenotypes. The perspective described in this paper is a modest step in that direction and, one hopes, a stimulus for further conceptual research and development.

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