Dysthymic Disorder: The Persistent Depression

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Cover Illustration by Kathryn K. Johnson
INTRODUCTION

Dysthymic disorder (DD) is a form of chronic depression that affects up to 6% of the general population and 5% to 15% of primary care populations. While the explicit etiology remains unknown, a variety of factors appear to contribute to this type of depression. DD is characterized by an insidious onset; waxing and waning symptomatology of at least 2 years' duration in adults and 1 year in children and adolescents; brief periods of euthymia; and symptoms that typically cluster around cognitive, social, and motivational areas. This form of depression is frequently comorbid with other medical and psychiatric disorders. Nearly all antidepressant trials have shown that patients benefit from these agents in varying degrees, and other forms of therapy are being investigated. However, the long-term outcome for sufferers of this disorder remains unclear.

EPIDEMIOLOGY

GENERAL POPULATION

The community prevalence of dysthymia in the United States varies depending on the source of the data. For example, according to data collected by the National Institute of Mental Health (1988) for the Epidemiological Catchment Area Study, the lifetime prevalence of DD in the general population is 3.1%. Kessler and colleagues, who reported on data from the National Comorbidity Survey in 1994, found the lifetime prevalence to be 4.8% among men and 8% among women (average, 6.4%). These latter findings echo the gender patterns typically observed in mood and anxiety disorders. Collectively, the data from these 2 large studies suggest that the lifetime prevalence of DD in the general population is approximately 3% to 6%. Narrow and colleagues reanalyzed these data and determined that the 1-year prevalence rate for dysthymia in the general population is 1.6%.

In addition to general population studies, nonclinical subpopulations have been examined. Among U.S. adolescents, the 1-year prevalence of dysthymia in a study by Garrison and colleagues was 3.4%. In a study examining Chinese Americans, Takeuchi and colleagues determined the lifetime prevalence of dysthymia as 5.2%. These rates are comparable with those reported for the broader population.

Do U.S. prevalence rates for dysthymia in the general population reflect international findings as well? The available studies are sparse. In a Norwegian study, the lifetime prevalence of dysthymia in the community was 5.9% among men and 13.3% among women (average, 10%). In a Swedish sample of very elderly individuals (aged 78–100 years), Forsell and colleagues found a current or point prevalence rate of 3.5%.

PRIMARY CARE POPULATION

According to Howland, the prevalence of dysthymia in U.S. primary care samples ranges from 1.3% to 31.9% (pooled prevalence rate of 7%). Spitzer and colleagues report that the majority of studies suggest that 5% to 15% of primary care patients suffer from DD. In addition, comparable rates have been found among low-income Mexican Americans in primary care settings.

In an international study of primary care patients, Lecrubier and Weiller examined the prevalence of dysthymia among 25,916 patients from 14 countries; the current or point prevalence rate was 2.1%. In a Canadian study, Browne and colleagues reported the 12-month prevalence of DD as 3.9% for men and 5.9% for women. In a Spanish sample, Ruiz-Doblado determined a current or point prevalence of approximately 0.5%. Baldwin summarized the international data and concluded that the point and lifetime prevalence rates for dysthymia were between 1.2% to 3.7% and 0.5% to 20.6%, respectively.

In mental health settings, Klein and colleagues and Markowitz and colleagues examined psychiatric outpatients for dysthymia and found prevalence rates of 22% and 36%, respectively.
SUMMARY

In the U.S. general population, the lifetime prevalence rate for dysthymia appears to be approximately 3% to 6%. The prevalence of dysthymia in U.S. primary care settings is higher than in the general population (5%–15%) and even higher in mental health settings (one quarter to one third of patients). The data from international general and primary care populations appear too limited to draw meaningful conclusions. When gender has been studied, the majority of investigations indicate higher prevalence rates in females compared with males.

ETIOLOGY

As with most psychiatric disorders, the explicit etiology of DD is unknown. It is likely that there are multiple contributory factors that may act alone or in concert to precipitate the symptoms of DD.

BIOLOGICAL ABNORMALITIES

Sleep abnormalities, often encountered in major depressive disorder (MDD), are found in 25% to 50% of adults with DD (eg, reduced rapid eye movement latency but increased density, reduced slow-wave sleep, impaired sleep continuity). Dysthymic individuals with polysomnographic abnormalities are more likely to have family histories of MDD and may respond better to antidepressants.

DD has been associated with elevated production of interleukin-1 in mitogen-stimulated lymphocytes and possible serotonergic dysfunction. Compared with males, platelet monoamine oxidase activity may be significantly lower in female patients with DD. Dexamethasone nonsuppression is uncommon in DD unless MDD also is present. Total testosterone levels may be lower in elderly men with DD compared with younger men with MDD and men without depressive symptoms. This suggests the possibility of hypothalamic-pituitary-gonadal axis hypofunction as a contributory factor in DD.

FAMILY STUDIES

DD is more common among the first-degree biological relatives of individuals with MDD. In addition, DD, MDD, and personality disorders are more common in the first-degree relatives of individuals with DD.

DIAGNOSIS

DD is characterized by a chronic, smoldering, low-grade dysphoric mood that lasts at least 1 year in children or adolescents or 2 or more years in adults (DSM-IV-TR Criterion A). During periods of depressed mood, at least 2 of the following additional symptoms are present: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty making decisions, and feelings of hopelessness (Criterion B). The depressive symptoms of DD tend to be cognitive (eg, low self-esteem, pessimism, feelings of inadequacy) rather than vegetative (eg, insomnia, loss of appetite). These symptoms often are accompanied by social withdrawal and low motivation.

According to the results of the DSM-IV mood disorders field trial, psychotic features are rare; there is no evidence of manic, mixed, or hypomanic episodes; and the dysphoria may be punctuated by brief periods of euthymia (up to 2 months per year). In children and adolescents, symptoms may include pessimism, low self-esteem, poor social skills, and irritability or crankiness. The essential defining feature of DD is the chronicity of depressive symptoms as well as significant morbidity. Impairment may occur in nearly all areas of life functioning. Because of the longstanding duration of symptoms, some individuals may misinterpret that “this is just how I am.”

DSM-IV-TR adds the following specifiers for DD: (1) early onset, for symptom onset before age 21 years; (2) late onset, for symptom onset at 21 years or older; and (3) with atypical features, if the symptom pattern includes mood reactivity and 2 other atypical symptoms (ie, weight gain or increased appetite, hypersomnia, leaden paralysis, interpersonal rejection sensitivity). The specifier of early-onset DD is especially important because of its association with particularly high rates of recurrence, subsequent episodes of MDD, comorbid personality disorders, psychiatric hospitalizations, and among women, low educational achievement, which may lead to underemployment and reduced income. Atypical features are more common in women and are associated with an earlier age of onset and more chronic course with only partial interepisode recovery.

HISTORICAL PERSPECTIVES

The term “dysthymia” was originally coined by Fleming in 1844. However, in the late 1880s, Kahlbaum was the first to develop a modern description of the disorder as a chronic, low-grade depression. In 1921, Kraepelin described “depressive temperament,” which he characterized as “a permanent, gloomy, emotional stress in all areas of life... they do not find complete, lasting satisfaction in their work, as they keep in view the mistakes and deficiencies of their achievements, as well
as approaching difficulties, rather than the value of the thing accomplished.”

Prior to the publication of the DSM-III29 in 1980, many clinicians conceptualized longstanding depression as characterologic in nature (eg, depressive neurosis and depressive personality disorder) and recommended long-term psychotherapy as the primary treatment. However, since the redefinition of chronic depression as an Axis I affective disorder, pharmacologic and psychotherapeutic research has been stimulated to improve the treatment of patients with DD. As an interesting compromise between the Axis I and II perspectives, Widiger30 maintains that DD should be viewed as a hybrid disorder, spanning the border between mood and personality disorders.

Diagnostic reorganization continues to underscore the heterogeneity of DD and all depressive disorders. With ongoing controversy concerning which criteria best define DD, DSM-IV-TR includes alternative criteria for DD as well as proposed diagnostic criteria for depressive personality disorder (Tables 1 and 2).17

It may be that the depressive disorders exist on a continuum with depressive personality disorder representing the early-onset variant. Other depressive disorders, which likely fall within the continuum, may include the criteria sets and axes for further study that are listed in appendix B of the DSM-IV-TR (eg, minor depressive disorder, recurrent brief depressive disorder, mixed anxiety-depressive disorder, postsychotic depressive disorder, premenstrual dysphoric disorder). These diagnoses currently would be categorized in DSM-IV-TR as depressive disorder not otherwise specified. Obviously, additional trials and evidence are needed to further clarify the boundaries of these mood disorders.

### Dysthymia Versus Major Depression: The Current Status

Given the historical evolution of dysthymia and major depression, the current differences are presented in Table 3. In MDD, there is a fairly well defined onset of symptoms compared with the typical insidious onset of symptoms in DD. MDD tends to manifest as discrete episodes, while DD has a more chronic and enduring course. MDD tends to be more symptomatically intense compared with the discreet cognitive, social, and motivational symptoms associated with DD. While the symptoms in MDD are sustained, DD may be interrupted by brief euthymic periods (< 2 months). Response to treatment is “good to excellent” in MDD, but only “fair” or incomplete in DD with two thirds of patients remaining symptomatic after 1 decade.31 Essentially, the clinical texture of these 2 types of depression is quite different and will undoubtedly evolve with future generations of DSM revisions.

### Comorbidity

“Pure” dysthymia, or dysthymia without any comorbid psychiatric or medical condition, is relatively rare. Indeed, it is so uncommon that the investigators participating in the National Institute of Mental Health

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**Table 1. DSM-IV-TR Alternative Research Criterion B for Dysthymic Disorder**

B. Presence, while depressed, of 3 (or more) of the following:
- Low self-esteem or self-confidence, or feelings of inadequacy
- Feelings of pessimism, despair, or hopelessness
- Generalized loss of interest or pleasure
- Social withdrawal
- Chronic fatigue or tiredness
- Feelings of guilt, brooding about the past
- Subjective feelings of irritability or excessive anger
- Decreased activity, effectiveness, or productivity
- Difficulty in thinking, reflected by poor concentration, poor memory, or indecisiveness


**Table 2. DSM-IV-TR Criteria for Depressive Personality Disorder**

A pervasive pattern of depressive cognitions and behaviors beginning by early adulthood and present in a variety of contexts, as indicated by 5 (or more) of the following:
- Usual mood is dominated by dejection, gloominess, cheerlessness, joylessness, unhappiness
- Self-concept centers around beliefs of inadequacy, worthlessness, and low self-esteem
- Critical, blaming, and derogatory toward self
- Brooding and given to worry
- Negativistic, critical, and judgmental toward others
- Prone to feeling guilty or remorseful

Does not occur exclusively during major depressive episodes and is not better accounted for by dysthyemic disorder

Collaborative Study on the Psychobiology of Depression had difficulty recruiting “pure” dysthymic subjects and had to change their methodology to acquire participants. Given the high level of comorbidity, the identification of these comorbid conditions may be clinically helpful in developing a course of treatment.

**COMORBID PSYCHIATRIC DISORDERS**

**MDD**

MDD is the most common comorbid Axis I disorder in those with DD. DD itself may be viewed as a risk factor for MDD; in clinical settings, up to 75% of individuals with DD develop MDD within 5 years. When MDD occurs in the course of DD, it is termed double depression, and the clinical course is characterized by high levels of depressive symptomatology, poor social adjustment, and global psychopathology.

**Anxiety Disorders**

Anxiety disorders are comorbid in approximately 50% of persons with DD. In a large series of primary care patients with DD, 90% screened positive for other Axis I disorders, which in addition to MDD included panic disorder, simple phobia, and generalized anxiety disorder. Up to 15% of dysthymic patients also have comorbid social phobia.

**Personality Disorders**

When comparing Axis II comorbidity between acute versus chronic depressives, chronic depressives demonstrate a higher prevalence, especially among those with early-onset DD (ie, 20%–40% higher). Associated personality disorders may include avoidant, dependent, self-defeating, histrionic, narcissistic, and borderline personality disorders. The presence of a personality disorder is related to more severe overall psychopathology.

**Somatoform Disorders**

Patients with somatoform disorders, such as somatization and hypochondriasis, have an increased rate of DD (2.8%–45.2%), underscoring the importance of depressive screening in this population.

**Substance Abuse**

As with all psychiatric disorders, substance abuse is often comorbid with DD. Since alcohol is one of the most potent depressive agents, it is imperative to routinely screen for substance abuse/dependence and appropriately address these issues.

**COMORBID MEDICAL DISORDERS**

Studies consistently indicate that dysthymia is significantly associated with poor health and that sufferers are likely to use 1.5 to 2 times as many medical services as nondepressed patients, even after controlling for chronic medical illness. Common co-occurring medical illnesses include neurologic conditions (eg, Parkinson’s disease, cerebrovascular disorders, multiple sclerosis, migraine headaches, and pain syndromes), sleep disorders, chronic fatigue, hypothyroidism, rheumatoid arthritis, and AIDS. Not all medical illnesses demonstrate this association, as indicated by the low rate of DD among cancer patients.

**COMORBIDITY IN CHILDREN AND ADOLESCENTS**

In children, DD may be associated with attention-deficit/hyperactivity disorder, conduct disorder, anxiety disorders, learning disorders, and mental retardation. Childhood and adolescent DD also is associated with a substantial risk for the later occurrence of both recurrent MDD and bipolar disorder.

**COMORBIDITY IN THE ELDERLY**

Midlife onset of DD appears to have less psychiatric comorbidity and more relationship to life stressors, particularly medical illnesses. These factors suggest a better overall prognosis. About one third of elderly dysthymic patients have personality disorders, with obsessive-

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**Table 3. Dysthymia versus Major Depression**

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Major Depression</th>
<th>Dysthymia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Well defined</td>
<td>Insidious</td>
</tr>
<tr>
<td>Criteria of symptom duration</td>
<td>2 weeks</td>
<td>2 years</td>
</tr>
<tr>
<td>Texture of symptoms</td>
<td>Intense, sustained symptoms</td>
<td>Smoldering, waxing and waning symptoms with brief periods of euthymia</td>
</tr>
<tr>
<td>Symptom constellation</td>
<td>Often psychomotor, appetite/weight and sleep changes</td>
<td>Often cognitive, motivational, social symptoms</td>
</tr>
<tr>
<td>Treatment response</td>
<td>Good to excellent</td>
<td>Fair, modest, high relapse rate</td>
</tr>
</tbody>
</table>
compulsive personality disorder being the most common, followed by avoidant personality disorder.52

TREATMENT

PHARMACOTHERAPY
Antidepressant Monotherapy

A multitude of studies have been undertaken to assess the efficacy of antidepressants in the treatment of DD (Table 4). A number of studies are double-blind or placebo-controlled, and nearly an equal number are open label. The majority of these studies include less than 50 subjects per study. While not evident in Table 4, the duration of trials varies from study to study, with few beyond 12 weeks. All of the studies indicate that many if not most patients respond to some degree to antidepressant treatment. This conclusion is supported by numerous authors.53–56 While only 1 study of monoamine oxidase inhibitors (MAOIs) is noted in Table 4, several authors affirm their efficacy in dysthymia as well.57–60 In addition, in their review of the available randomized controlled drug trials for the treatment of dysthymia (n = 15 and 16, respectively), Lima and Moncrieff61 and de Lima and Hotopf62 conclude that the efficacy among the different groups of antidepressant drugs is similar.

Despite the potential effectiveness of antidepressant therapy in the treatment of dysthymia, there is controversy about the genuine robustness of responses with medications. In this regard, Howland63 acknowledges that the antidepressant response in DD is typically less robust than that found in major depression. Fawcett64 confirms that while most studies affirm improvement, scores on rating scales indicate that at the end of treatment trials, many patients experience only a partial response and fail to achieve a full remission. Therefore, while antidepressant medication is clearly helpful, many patients do not experience full remission. The genuine extent of these modest or partial responses to antidepressants among dysthymic patients is unknown.

As for an antidepressant strategy, treatment algorithms are available.64,65 Regardless, the initial use of selective serotonin reuptake inhibitors (SSRIs) can be justified based upon their broad clinical efficacy with a variety of symptoms or disorders other than depression including anxiety, social phobia, panic attacks, impulsivity, worry, posttraumatic stress, obsessive-compulsive disorder, bulimia nervosa, and premenstrual dysphoric disorder.66 This seemingly unique feature of SSRIs may be particularly useful given the observation that DD is highly comorbid with other psychiatric disorders. However, this rationale does not preclude the use of other antidepressants as initial treatment choices. In addition, side effect profiles and patient characteristics are relevant factors in initial drug selection.

Should an initial antidepressant trial be unsuccessful, changing to an antidepressant with a different mode of neurotransmitter activity appears logical.67 Indeed, Thase and colleagues68 found that nonresponders who were switched from sertraline to imipramine, or vice versa, experienced a clinical improvement 50% of the time.

Because dysthymia is a chronic form of depression, patients may require longer drug-evaluation trials than those observed in major depression.69,70 Kocsis70 indicates that a substantial number of patients experience initial partial remission but with time report greater remission, reinforcing the concept of longer drug-evaluation trials. Twelve-week trials are recommended.64,71 Because few patients have robust responses with antidepressant monotherapy, it may be difficult to determine what is an acceptable response at the 12-week juncture.

In addition to the preceding guides, various authors have broached management suggestions in the pharmacotherapy of dysthymia. In this regard, Dunner72 emphasizes the importance of higher doses of medication and longer treatment than that required for major depression. Frances73 acknowledges the risk of patient sensitivity to side effects, implying the need to be cautious with dose increases. This is a particular concern among dysthymic patients with Axis II comorbidity and/or early-onset dysthymia. Kornstein and colleagues74 suggest that women may be more likely to respond to SSRIs and men to tricyclic antidepressants. Finally, Baldwin14 recommends that antidepressant therapy be undertaken in conjunction with psychological therapies.

Augmentation Strategies

Kocsis70 underscores that fewer than 50% of patients achieve a full remission with a single agent. Should prescribers initiate a change in antidepressants? According to Posternak and Zimmerman,75 switching antidepressants may be somewhat less effective than an augmentation strategy. This suggests that combinations of medications be considered, although a well-defined, empirically determined strategy remains elusive. Note that many of the augmentation strategies discussed in the empirical literature refer to refractory depression but also may be used in the treatment of dysthymia.

Medications used for the augmentation of treatment-resistant depression include lithium,76,77 psychostimulants such as methylphenidate,78 dextroamphetamine,78 and modafinil,79,80 gabapentin,81,82 buspirone,83–86 and pindolol.87 Several studies also indicate that thyroxine,88,89
Table 4. Published United States Studies of Antidepressants in the Treatment of Dysthymia or Chronic Depression

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>First Author</th>
<th>Year</th>
<th>N*</th>
<th>Study Description</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MAOIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moclobemide</td>
<td>de Mello</td>
<td>2001</td>
<td>35</td>
<td>Randomized</td>
<td>Significant improvement</td>
</tr>
<tr>
<td><strong>TCAs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>Stewart</td>
<td>1985</td>
<td>16</td>
<td>DB, PC</td>
<td>Desipramine = placebo</td>
</tr>
<tr>
<td></td>
<td>Marin</td>
<td>1994</td>
<td>75</td>
<td>Open label</td>
<td>70% response</td>
</tr>
<tr>
<td></td>
<td>Friedman</td>
<td>1995</td>
<td>12</td>
<td>Open label, retreatment</td>
<td>92% full remission</td>
</tr>
<tr>
<td></td>
<td>Kocsis</td>
<td>1996</td>
<td>129</td>
<td>Open label, placebo phase</td>
<td>Desipramine &gt; placebo</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Kocsis</td>
<td>1988</td>
<td>22</td>
<td>DB, PC</td>
<td>Imipramine &gt; placebo</td>
</tr>
<tr>
<td></td>
<td>Bakish</td>
<td>1994</td>
<td>16</td>
<td>DB, PC</td>
<td>Imipramine &gt; placebo</td>
</tr>
<tr>
<td></td>
<td>Salzmann</td>
<td>1995</td>
<td>34</td>
<td>DB, PC</td>
<td>Imipramine &gt; placebo</td>
</tr>
<tr>
<td></td>
<td>Thase</td>
<td>1996</td>
<td>91</td>
<td>DB, PC</td>
<td>Imipramine &gt; placebo</td>
</tr>
<tr>
<td></td>
<td>Versiani</td>
<td>1997</td>
<td>103</td>
<td>DB, PC</td>
<td>Imipramine &gt; placebo</td>
</tr>
<tr>
<td></td>
<td>Kocsis</td>
<td>1997</td>
<td>136</td>
<td>DB, PC</td>
<td>64% response</td>
</tr>
<tr>
<td><strong>SSRIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>Zanalda</td>
<td>1998</td>
<td>20</td>
<td>Open label</td>
<td>Improvement</td>
</tr>
<tr>
<td></td>
<td>Dunner</td>
<td>2002</td>
<td>15</td>
<td>Open label</td>
<td>Majority responded</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Rosenthal</td>
<td>1992</td>
<td>12</td>
<td>Open label, randomized</td>
<td>71% response average</td>
</tr>
<tr>
<td></td>
<td>Hellerstein</td>
<td>1993</td>
<td>16</td>
<td>DB, PC</td>
<td>62.5%, fluoxetine &gt; placebo</td>
</tr>
<tr>
<td></td>
<td>Bakish</td>
<td>1994</td>
<td>34</td>
<td>Open label</td>
<td>Symptom reduction</td>
</tr>
<tr>
<td></td>
<td>Ravidran</td>
<td>1994</td>
<td>52</td>
<td>Open label</td>
<td>73% response, &gt; in females</td>
</tr>
<tr>
<td></td>
<td>Nobler</td>
<td>1996</td>
<td>23</td>
<td>Placebo run-in</td>
<td>60% response</td>
</tr>
<tr>
<td></td>
<td>Vanelle</td>
<td>1997</td>
<td>91</td>
<td>DB, PC</td>
<td>Fluoxetine &gt; placebo</td>
</tr>
<tr>
<td></td>
<td>Waslick</td>
<td>1999</td>
<td>19</td>
<td>Open label, children</td>
<td>73% response</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>de Jonghe</td>
<td>1991</td>
<td>26</td>
<td>DB, randomized</td>
<td>Modest improvement</td>
</tr>
<tr>
<td></td>
<td>Rabe-Jablonska</td>
<td>2000</td>
<td>21</td>
<td></td>
<td>56% response</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Ballus</td>
<td>2000</td>
<td>43</td>
<td>Randomized</td>
<td>29% response</td>
</tr>
<tr>
<td></td>
<td>Nobile</td>
<td>2000</td>
<td>7</td>
<td>Open label, age &lt; 18</td>
<td>71% response</td>
</tr>
<tr>
<td></td>
<td>Rocca</td>
<td>2002</td>
<td>28</td>
<td>Open label, randomized</td>
<td>54% response</td>
</tr>
<tr>
<td>Paroxetine + Amisulpride</td>
<td>Rocca</td>
<td>2002</td>
<td>32</td>
<td>Open label, randomized</td>
<td>56% response</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Thase</td>
<td>1996</td>
<td>113</td>
<td>DB, PC</td>
<td>Sertraline &gt; placebo</td>
</tr>
<tr>
<td></td>
<td>Chinchilla</td>
<td>1997</td>
<td>50</td>
<td>Open label</td>
<td>Improvement</td>
</tr>
<tr>
<td></td>
<td>Ravidran</td>
<td>2000</td>
<td>158</td>
<td>DB, PC</td>
<td>33%–47% improved scores</td>
</tr>
<tr>
<td></td>
<td>Amoore</td>
<td>2001</td>
<td>150</td>
<td>DB</td>
<td>69% response</td>
</tr>
<tr>
<td></td>
<td>Nixon</td>
<td>2001</td>
<td>8</td>
<td>Open label</td>
<td>67% response</td>
</tr>
<tr>
<td></td>
<td>Kocsis</td>
<td>1997</td>
<td>134</td>
<td>DB, PC</td>
<td>59% response</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazepine</td>
<td>Dunner</td>
<td>1999</td>
<td>15</td>
<td>Open label</td>
<td>Effective</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Dursun</td>
<td>2002</td>
<td>6</td>
<td>Pilot study</td>
<td>Improvement</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Rosenthal</td>
<td>1992</td>
<td>8</td>
<td>Open label, randomized</td>
<td>71% response average</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Hellerstein</td>
<td>2001</td>
<td>21</td>
<td>Open label</td>
<td>71% response, &lt; with substance abuse</td>
</tr>
</tbody>
</table>

NOTE: For studies comparing 2 drugs, individual drugs are listed. This contains the majority of pharmacologic studies for the treatment of dysthymia and chronic depression; however, studies beyond PsycINFO, MEDLINE, or those reported at meetings may not be included. (DB = double-blind; MAOI = monoamine oxidase inhibitor; PC = placebo-controlled; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.)

*NNumber of subjects on active drug.
and triiodothyronine augmentation may improve depressive symptoms. Indeed, one group of French investigators routinely supplements thyroid hormones in patients who are in the upper 25th percentile of normal thyroid-stimulating hormone range to achieve an antidepressant response.

The use of low-dose, atypical antipsychotic medications is another consideration. The effectiveness of olanzapine and risperidone is noted in the literature. This does not exclude the possibility of using other atypical antipsychotic drugs, and there are few comparison trials.

Combining antidepressants is another possible option. Lam and colleagues reviewed 27 studies of combined antidepressant treatment and concluded that the overall response rate for this type of augmentation was 62.2%. However, the risks of particular antidepressant combinations (eg, MAOIs and other antidepressants, bupropion and antidepressants that may inhibit its metabolism through the 2B6 isoenzyme, SSRIs and tricyclic antidepressants) have not been well elucidated.

Finally, some studies suggest mood benefits with the addition of vitamins or other naturally occurring substances. Examples include folate, chromium, and omega-3 fatty acids (but not docosahexaenoic acid).

At the present time, no empirically confirmed strategy for augmentation is known. We suggest weighing the potential benefits and risks in individual patients and attempting lower-risk interventions at the outset. For healthier outpatients, these may include the addition of folate, eicosapentaenoic acid, buspirone, gabapentin, and low-dose atypical antipsychotics, with subsequent consideration of dual antidepressants, lithium, and other anticonvulsants.

### Nonpharmacologic Interventions

In addition to medications, nonpharmacologic interventions have been utilized in the treatment of dysthymia including cognitive behavioral treatment, interpersonal therapy, manualized group therapy, problem-solving therapy, and exercise. While it is not entirely clear if there are any specific advantages to one intervention over another, or whether specific subpopulations of patients are more likely to respond to one treatment over another, cognitive approaches have been the most frequently studied and appear promising.

As a caveat, few empirical data exist on the combination strategy of medication and nonpharmacologic intervention. In a study of chronic major depression, Keller and colleagues found that in comparison with either treatment, the combination of drug treatment (in this case, nefazodone) and a version of cognitive therapy offered the maximum benefit to patients. Whether these findings might apply to dysthymic patients remains unknown. However, other authors support combination therapy in the treatment of dysthymia.

### Outcome and Prognosis

Long-term outcome studies (ie, those longer than 12 months) among dysthymic patients are scarce (Table 5). In addition, these studies are difficult to interpret because of the various measures used for recovery, as well as the different types of study populations (eg, private practice, elderly). However, one theme emerges from this overview—a substantial number of sufferers do not experience a sustained recovery. Indeed, even among those who experience remission, there is a reasonable risk of relapse. We are not aware of any empirical evidence that suggests that dysthymic symptoms diminish or burn out with age. Collectively, these findings suggest that, for many individuals, dysthymia will be a chronic and perhaps lifelong disorder that undergoes exacerbations and remissions throughout the life cycle.

Specific variables may affect the course of the disorder. One study examined the role of life stressors among those diagnosed with DD and investigators concluded that life events, particularly new-onset stressors or the combination of new-onset and chronic stressors, play a meaningful role in precipitating major depressive episodes. In addition, early-onset dysthymia may be a marker for recurrent affective disorders in adulthood. Almost all patients with dysthymia eventually experience major depressive episodes. The relationship between the onset of dysthymia and major depression also may have an influence on prognosis. The onset of the first episode of dysthymia after a major depression, rather than before or concurrently, may indicate a more adverse course.

As for prognostic indicators, early-onset dysthymia appears to be associated with a less favorable outcome and may require a longer recovery time. This is in line with our clinical experience, which suggests that early-onset dysthymia is more difficult to treat and less likely to have robust responses to treatment, compared with late-onset dysthymia. Indeed, those with late-onset dysthymia and a good premorbid psychiatric adjustment may fare very well.

As for other prognostic indicators, demographic and other clinical variables are not strong predictors of outcome. However, according to Durban and colleagues, negative predictors may include a childhood...
history of sexual abuse, poor relationships with both parents, and family histories of drug abuse and/or Cluster A personality disorders. According to Hayden and Klein,\(^1\) comorbid anxiety disorders, Cluster C personality features, chronic stress, and eating disorders also may be associated with lower rates of recovery and higher levels of depression at follow-up.

**SUMMARY**

DD is a common form of depressive illness. While the explicit etiology remains unknown, the diagnosis is dependent upon a minimal 2-year duration and a symptom presentation that may appear quite different than major depression. The disorder is highly comorbid with other psychiatric and medical disorders, particularly major depression. In the approach to treatment, antidepressant monotherapy is the initial approach, but the clinician should anticipate the need for combination medications (ie, augmentation strategies). There is no consensus regarding an augmentation algorithm. The outcome of dysthymia remains somewhat controversial. While most patients experience clinical improvement with treatment, unfortunately many may not fully recover and relapses and recurrences may be the rule rather than the exception.

**REFERENCES**

18. Anisman H, Ravindran AV, Griffiths J, Merali Z. Interleukin-

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**Table 5. Outcome Studies in Dysthymia with More Than 1-Year Follow-up**

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>n</th>
<th>Study Description</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kivela</td>
<td>1993</td>
<td>199</td>
<td>5-year, naturalistic follow-up of elderly sample (aged 60–94)</td>
<td>29% males, 39% females recovered</td>
</tr>
<tr>
<td>Oldehinkel</td>
<td>1999</td>
<td>61</td>
<td>20-month follow-up of community sample of adolescents</td>
<td>33% remission</td>
</tr>
<tr>
<td>Haykal</td>
<td>1999</td>
<td>42</td>
<td>5-year follow-up of psychiatric outpatients on fluoxetine</td>
<td>Sustained response rate of 76% with antidepressants</td>
</tr>
<tr>
<td>Klein</td>
<td>2000</td>
<td>86</td>
<td>5-year, naturalistic follow-up of early-onset, dysthymic psychiatric outpatients</td>
<td>Recovery rate = 52.3%; among recoveries, 45.2% relapse</td>
</tr>
</tbody>
</table>
Dysthymic Disorder: The Persistent Depression

Dysthymic Disorder: The Persistent Depression


106. de Mello MF, Myczowisk LM, Menezes PR. A randomized controlled trial comparing moclobemide and moclobemide plus...


