The Long-Term Outcome of Dysthymia in Private Practice: Clinical Features, Temperament, and the Art of Management

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Background: With the clinical availability of fluoxetine in the United States, we were interested in documenting improvements in the clinical care of dysthymic patients beyond what was reported from our clinic 2 decades earlier during the "tricyclic (TCA) era."

Method: In open treatment of 42 consecutive DSM-III-R primary dysthymic patients who were personally followed up in our mood clinic since 1988, response was defined as sustained remission, i.e., no longer meeting criteria for dysthymia and achieving DSM-III-R Axis V Global Assessment of Functioning (GAF) score > 70 throughout much of the mean follow-up of 5 years.

Results: Compared to patients with nondysthymic episodic major depressive disorder (N = 42), dysthymic patients had a significantly earlier mean age at onset (12.6 vs. 34 years), were more likely to have never been married, had a greater frequency of superimposed major depressive episodes (except for the 14% [N = 6] with "pure" dysthymia), and had more psychiatric and fewer medical comorbidities; furthermore, patients with dysthymia had significantly greater familial loading of both unipolar and bipolar disorders. Continued treatment with TCA-type antidepressants or fluoxetine (including various augmenting strategies) led to an overall robust and sustained response rate of 76% (N = 32) among dysthymic patients; in tandem, major depressive episodes and suicidality were prevented in all responders. Females treated with fluoxetine had the highest response rate (85% [N = 17]); some were able to walk out of dependent abusive relationships for the first time in their lives. However, dramatic responses with "hyperthymic" switches in temperament occurred in only 12% of dysthymic patients; nearly all were males with bipolar family history. The more prototypic positive change among dysthymic responders consisted of coping with daily hassles without being overwhelmed. Qualitatively, the highest level of adaptive functioning was observed among fluoxetine-treated dysthymics (50% of responders [N = 12] achieved DSM-III-R GAF score of 81–90). Of TCA-treated patients, 39% had intolerable side effects, necessitating switch-over to fluoxetine. Agitation occurred in 11% of fluoxetine-treated patients (N = 4) and was associated with nonresponse and/or dropout; otherwise, this selective serotonin reuptake inhibitor was well tolerated, thereby contributing to long-term compliance. More provocatively, patients with dysthymia who had required extensive psychotherapeutic attention prior to state-of-the-art pharmacotherapy no longer required such therapy.

Conclusion: These data extend and enrich what has been learned from controlled trials among dysthymic patients. With sustained pharmacotherapy and specialized clinical care in a private mood clinic, 3 of 4 patients immersed in gloom for much of their lives achieved for the first time good to superior levels of functioning that were maintained for an average of 5 years. Although the art of clinical management of dysthymia should be fully grounded in understanding the interpersonal context of depression, we submit that SSRIs such as fluoxetine appear broadly efficacious in areas previously deemed to be the domain of formal psychotherapy.

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Every task stands in front of them like a mountain; life with its activity is a burden which they habitually bear with dutiful self-denial without being compensated by the pleasures of existence. . . . They have "very little vital energy," they despair at every task, and become anxious and despondent with extreme facility . . . they feel themselves good for nothing . . . regard themselves as nature's step children . . . they are without initiative, uncertain, they ask for advice on the slightest occasion.

—Emil Kraepelin[1]

Current data indicate that so-called "minor," dysthymic or otherwise subthreshold depressions are associated with considerable morbidity, comorbidity, and functional impairment.[2–5] This is largely due to the protracted, intermittent or chronic nature of these conditions, of which the most studied entity is dysthymia. This disorder was introduced into the official American Psychiatric

Association (APA) nomenclature in 1980[6] and in the International Classification of Diseases (ICD-10) in 1992.[7] In their habitual self, these patients exhibit chronic or intermittent low-grade depressive symptomatology of insidious onset often dating to early life. Our 1980 open observation of thymoleptic response[8] has been replicated in double-blind trials,[9,10] demonstrating low rates (12%–17%) of placebo response compared with significantly higher rates of response to imipramine and phenelzine (ranging, respectively, from 45%–70%), and considerable attenuation of characterologic and social disturbances with extended treatment beyond the acute protocol. Despite such gains in our therapeutic armamentarium against chronic depression, autonomic side effects and weight gain are often problematic with tricyclic antidepressants. Hence the current shift of interest to newer agents: the reversible monoamine oxidase inhibitor moclobemide,[11] the atypical neuroleptic amisulpride[12,13]—both presently unavailable for clinical use in the United States—and selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine[14,15] and sertraline.[16]

Despite the increasing methodologic sophistication of acute phase controlled trials,[17] open extension of pharmacotherapy over 18 months reveals success rates of approximately 50%.[18] How patients in actual treatment settings fare is presently unknown. As our 1992 2-year outcome results with fluoxetine were encouraging (especially in women),[19] in this article we are reporting 5-year data from our open systematic longitudinal study. To properly assess the impact of emerging pharmacologic approaches on the outcome of dysthymia, we examined in great detail the clinical picture, temperamental aspects, comorbidity, familial background, gender issues, and the prospective course of this disorder in a well-defined core group of dysthymic patients. In reporting our findings, one of our main objectives is to illustrate the clinical management of dysthymia with state-of-the-art approaches that have evolved in our specialized mood clinic program. The present report focuses on fluoxetine, because it has been available the longest in the United States, and we could pull long-term clinical data on a sufficiently large cohort.

PATIENTS AND METHOD

Diagnostic Procedures

The 42 consecutive adult (≥ 18 years) outpatients with primary dysthymia at index evaluation were all enrolled in our mood disorders program, which consists of an interwoven network of university- and private hospital–based mood clinics. Their low-grade depressive symptomatology began insidiously, was not a sequel to major depressive episodes, and represented the habitual self of the patient. We excluded those with past history of unequivocal hypomanic or manic episodes and those with chronic psychotic disorders. Because the main objective of the present study is to characterize primary dysthymic disorder from clinical and therapeutic standpoints, comorbid conditions such as panic attacks, bulimia, and substance abuse were permitted if they did not dominate the clinical picture.

Clinical assessment in our program is based on the Mood Clinic Data Questionnaire (MCDQ), a semistructured tool developed at the University of Tennessee.[20] The diagnostic criteria derived from Feighner et al.[21] are enriched with affective spectrum diagnoses (e.g., dysthymia and depressive temperaments). Diagnosis conforms to the DSM-III-R definition of dysthymia.[22] Depressive temperament[23] is operationally defined by a modification of Schneider's[24] description (≥ 5 needed): (1) gloomy, pessimistic, humorless, or incapable of fun; (2) quiet, passive, and indecisive; (3) skeptical, hypercritical, or complaining; (4) brooding and given to worry; (5) conscientious or self-disciplining; (6) self-critical, self-reproaching, and self-derogatory; and (7) preoccupied with inadequacy, failure, and negative events to the point of morbid enjoyment of one's failures. (The distinction between dysthymia and depressive temperament has been found to be valid.[25,26]) As for Axis II descriptors (DSM-III-R), we opted on clinical grounds to assign the dominant personality at the trait level—1 item less than the threshold—and above. We are aware that, except for depressive personality,[25] the reliability of individual Axis II constructs leaves much to be desired. For this reason, in the results we will describe them by cluster and not subject them to statistics.

Clinical diagnoses (both Axis I and Axis II) were based on patient interview conducted by one of us, plus examination of all available clinical information from past records and significant others. For final inclusion of a patient in the study, after examining all the clinical findings, both authors had to reach 100% consensus on each case as representing "primary" dysthymia. The thrust of these procedures was to limit inclusion to a strictly defined dysthymic group and to assure that if major depressive episodes were superimposed, they arose from a well-established dysthymic baseline. Superimposed major depressive episodes were diagnosed only when the symptomatic level had so accentuated as to meet the DSM-III-R threshold, concomitant with deterioration of social and/or vocational functioning from that of the dysthymic baseline. For selected comparisons, we identified 42 consecutive nonbipolar patients with episodic major depressive disorder but without dysthymia—from the same clinical settings—with comparable index age (± 5 years).

Family history was based on Winokur's approach as incorporated into the Research Diagnostic Criteria (FH-RDC)[27]: we focused on major mood disorder subtypes, alcoholism, and suicide. All data are on first-degree adult relatives. Two thirds of the relatives were patients under our care or were available for direct interview; hence, much of the familial data consist of diagnoses vali-

dated by follow-up care. A hierarchy was used in reporting percentages of patients with familial mood disorder whereby the presence of bipolar illness in the same lineage precluded counting any patient with coexisting major depressive disorder; in other words, patients with unipolar illness in a given lineage were counted only in the absence of bipolar illness. This approach is justified inasmuch as we sought to identify the proportion of dysthymic patients who came from bipolar versus unipolar pedigrees.

Patients enrolled in our clinical program routinely provide consent as required in each of its component clinics and by Institutional Review Boards for the protection of human subjects.

Course and Treatment Outcome

Given the difficulty of dating age at onset in an insidious illness, for the majority who could not pinpoint a specific age at onset, we asked them to approximate it in the following ranges: 6–9, 10–13, 14–17, or 18–21 years. They were then asked to identify a major milestone in their lives and date dysthymic symptomatology vis-à-vis that event. Patients were followed up for a mean ± SD of 55.2 ± 36.9 months.

Treatment was clinician's choice open design. Maintenance treatment in all instances was with antidepressants and thymoleptic agents as warranted clinically and at dosage levels tolerated by each patient. In line with established routines in our program, all patients received supportive psychotherapy and psychoeducation at one phase or another; more formal psychotherapy such as individual psychodynamic therapy, group cognitive-behavior therapy, or conjugal therapy was provided to the few who needed it.

Response was defined conservatively as unequivocal clinical improvement with a DSM-III-R Global Assessment of Functioning (GAF) score of > 70 sustained beyond 6 months; this also meant that patients no longer met the symptomatologic criteria for dysthymia. We used this stringent criterion to assure that the response was not merely part of the natural fluctuation of the habitual dysthymia in and out of major depression and that the improvement in dysthymic symptomatology was of such a magnitude that it was reflected in a sustained qualitative change in functioning. GAF scores were obtained during prospective follow-up visits, which varied in frequency depending on clinical necessity. Conservatively, all those who dropped out of treatment before showing such sustained improvement were counted as treatment failures.

Statistical Procedures

Statistical comparisons were made between the dysthymia and episodic major depressive disorder groups, as well as between the responder and nonresponder subgroups of dysthymic patients, on several demographic and clinical parameters. Categorical data were compared using either chi-square (with Yates correction, when necessary) or r × c tables with Miller's[28] follow-up method for more than 2 variables. Fisher exact statistics were used when indicated. Student t test statistics were reserved for continuous data. We conservatively used 2-tailed statistics. The statistical tests within the dysthymic group are post hoc without a priori hypotheses and are cited for illustrative purposes only.

RESULTS

Demographic Characteristics

Continuous variables are expressed as mean ± SD. Dysthymic patients had a mean index age of 34.8 ± 11.9 years, evenly divided between male and female. With respect to marital status, 55% (N = 23) of the dysthymic group were currently married, 12% (N = 5) separated or divorced, and 33% (N = 14) were never married; mean number of marriages was 1.29 ± 0.46. We compared these demographic variables with those of the nondysthymic patients with episodic major depressive disorder. By inclusion requirements, the index age of 38.0 ± 8.8 years for the patients with episodic major depressive disorder was comparable to that of dysthymic patients ($F = 1.93$, $df = 1,82$; $p = NS$). The sex ratio of 3:1 in favor of female among patients with episodic major depressive disorder was statistically different from the 1:1 ratio among patients with dysthymia ($\chi^2 = 5.05$, $df = 1$, $p = .025$). We then compared the 2 groups on marital status: dysthymic patients were more likely to never marry than patients with episodic major depressive disorder (33% vs. 3%, $\chi^2 = 13.88$, $df = 2$, $p < .001$).

Age at Onset and Past Course

Although 50% (N = 21) had past psychiatric hospitalizations for major depressive episodes, all dysthymic patients entered the present study as outpatients. Only 14% (N = 6) had never had any discernible major episodes; 19% (N = 8) had had a single episode, 12% (N = 5) had had 2 episodes, and the majority (55% [N = 23]) had had 3 or more episodes. By contrast, among the patients with episodic major depressive disorder, the majority had 1 episode (55% [N = 23]), 26% (N = 11) had 2 episodes, and only 19% (N = 8) had 3 or more episodes ($\chi^2 = 16.40$, $df = 2$, $p < .001$).

Nearly two thirds of the dysthymic patients (N = 14) had their onset at puberty or before (33% at 6–9 years and 29% at 10–13 years); onset in the remaining was at 14 to 17 years in 24% (N = 10), and above age 18 in 14% (N = 6); only 1 of the latter patients (2% of the total) developed dysthymia after age 25 (specifically at age 27). The mean age at onset of 12.6 ± 5.5 years for patients with dysthymia was significantly younger than that of 34.0 ± 8.3 years for patients with episodic major depressive disorder ($F = 194.66$, $df = 1,82$; $p < .0001$). Despite

such early onset of low-grade depressive symptomatology in the dysthymic group, the mean age at which patients first sought professional help was 27.7 ± 9.6 years, and first psychiatric contact was at age 29.5 ± 9.0 years. Thus, dysthymic patients waited for an average of 15.1 ± 10.6 years before seeking help, compared with 1.9 ± 4.8 years in their nondysthymic counterparts with episodic major depressive disorder ($t = 7.35$, $df = 57.34$, $p < .0001$).

Prior to referral to us, most dysthymic patients had received either psychotherapy (36%, N = 15) or no treatment at all (21%, N = 9); the remaining 43% (N = 18) had received primarily 1 or 2 trials of tricyclic antidepressants (TCAs) at essentially subtherapeutic doses (e.g., less than imipramine equivalent of l50 mg).

Clinical Manifestations

Core manifestations observed or reported by more than two thirds of dysthymic patients included the following: in the domain of mood, gloominess, irritable morosity, and joyless existence; low self-esteem, guilty ruminations, brooding, pessimistic outlook, and thoughts of death dominated the cognitive realm; asthenia, inertia, sluggishness, and social withdrawal characterized the psychomotor sphere; and lethargy with classic diurnality (i.e., inertia and gloominess worse in the a.m.) represented the main "vegetative" disturbances. It is noteworthy that most of these manifestations are more in the subjective and cognitive realms, yet they include such classic "endogenous" features as anhedonia and diurnality. Weight gain occurred in 48% (N = 20) of patients with dysthymia; but as many as 29% (N = 12) lost weight, which, in most instances, occurred during superimposed major depressive episodes. Transition to major depressive episodes was further heralded by middle or terminal insomnia, poor concentration, observed retardation, inability to function, hopelessness, and intense preoccupation with suicide.

Ten patients with dysthymia (24%) had a history of suicidal behavior as compared with only 3 patients in the episodic major depressive disorder group (7%) ($\chi^2 = 7.84$, $df = 2$, $p < .02$). This may in part be due to the fact that the dysthymic patients, having been ill longer, had engaged in more suicidal behavior.

Fall-winter accentuation of dysthymia occurred in 7 female and 3 male patients (24%). Marked premenstrual accentuation of dysthymic symptomatology for about as long as 1 week occurred in 67% (N = 14) of women.

Personality

Of Axis II descriptors, most patients with dysthymia (83% [N = 35]) fell into the "anxious cluster," with far fewer (17% [N = 7]) in the "dramatic cluster." A similar pattern could be seen in the patients with episodic major depressive disorder (86% [N = 36] in the anxious cluster). Fifty percent of the patients with dysthymia (N = 21) met the criteria for depressive temperament (48% female [N = 10], 52% male [N = 11]). This temperament overlapped highest with the avoidant (8 of 8), followed by dependent (9 of 12), less with the obsessive (4 of 13), and not at all with dramatic traits.

Family History

We compared 41 dysthymic patients (omitting the 1 patient who was adopted) with 41 of the matched nondysthymic patients with episodic major depressive disorder. The respective rates were as follows: bipolar (24% vs. 3%), unipolar (61% vs. 24%), and alcoholism (10% vs. 29%) ($\chi^2 = 29.39$, $df = 2$, $p < .0001$).

Associated Features

By entry criteria, we had excluded patients whose illness was dominated by nonmood disorders, yet the course of dysthymia was punctuated by the intermittent appearance of various other Axis I symptomatologies in 55% (N = 23). These included alcohol (17%), caffeine (12%, as defined by Greden and Walters[29]), and marijuana (5%) abuse, bulimia (14%), as well as social phobia (19%) and panic attacks (10%). Although 45% of dysthymic patients (N = 19) exhibited excessive worrying, they did not otherwise meet the strict criteria for generalized anxiety disorder. Likewise, we did not diagnose generalized anxiety disorder in patients with episodic major depressive disorder, because of the redundancy involved. As for Axis I comorbidity in the episodic major depressive disorder group, 12% had alcohol abuse, 2% caffeine abuse, 2% polysubstance abuse, 5% somatization hysteria, and 5% panic disorder (the total of 26% was significantly less than that of 55% in the dysthymic group, $\chi^2 = 5.98$, $df = 1$, $p < .05$).

Concurrent Physical Illness

Five dysthymic patients (3 women and 2 men) had borderline hypothyroidism as defined by Extein and Gold,[30] and 2 had hypothyroidism secondary to past surgery or irradiation (total with thyroid disturbance = 17% [N = 7]). In addition, 1 patient had chronic uropathy, 1 had history of subdural hematoma evacuated by surgery, 1 had had chemotherapy for lymphoma, and 1 had essential hypertension. Axis III comorbidity in patients with episodic major depressive disorder included 8 with essential hypertension, 3 with hypothyroidism, 3 with recurrent urinary tract infection, 3 with peptic ulcer disease, and 1 each with cytomegalovirus hepatitis, infectious mononucleosis, psoriasis, and polycystic ovarian disease (the total of 50% was significantly greater than that of 26% in the dysthymic group, $\chi^2 = 4.07$, $df = 1$, $p < .05$).

Outcome

Seventeen dysthymic patients were started on fluoxetine therapy de novo, i.e., no past treatment with any antidepressants; 23 patients were given TCAs at some phase in their treatment, and the remaining 2 patients were

treated with the monoamine oxidase inhibitor (MAOI) phenelzine. Of the 23 TCA-treated patients, 18 were later placed on fluoxetine—either because of nonresponse (N = 9) or because of intolerable side effects (anticholinergic, N = 4; weight gain, N = 4; ECG changes, N = 1)—raising fluoxetine-treated patients to 35. Judgment of TCA nonresponse and intolerable side effects was based on at least 8 weeks of treatment.

Twenty-four (69%) of the 35 fluoxetine-treated patients responded with GAF scores > 70, compared with 12 (52%) of 23 TCA-treated patients. Although these overall response rates by drug were not statistically significant, drug response analyses by gender showed significant differences. Thus, within the fluoxetine group, 17 (85%) of 20 females responded, while only 7 (47%) of 15 males were fluoxetine responders (Fisher exact test, p = .027). Among the TCA-treated patients, 5 (45%) of 11 females responded, as compared to 7 (58%) of 12 males (Fisher exact test, p = .728). All 9 patients (100%) who previously responded to a TCA and then were switched to fluoxetine because of side effects also responded to fluoxetine. Six (67%) of 9 TCA nonresponders had good response to fluoxetine.

Pretreatment-GAF scores for the entire dysthymic sample were 51.74 ± 6.12 for the fluoxetine-treated subgroup versus 50.43 ± 6.90 for the TCA-treated subgroup; posttreatment-GAF scores were 71.06 ± 10.88 for the fluoxetine subgroup versus 64.39 ± 9.16 for the TCA subgroup. Among responders, posttreatment-GAF scores were 77.67 ± 4.44 for fluoxetine versus 72.0 ± 1.81 for TCA. All (12/12) posttreatment-GAF scores among the responders in the TCA group were in the 71–80 range. In the fluoxetine group, the posttreatment-GAF scores among 12 responders rose to 71–80 and among another 12 rose higher, 81–90. An interesting finding among 12% (N =5) of the fluoxetine-responsive dysthymic patients (which was not observed in TCA-responsive dysthymic patients) was hyperbolic statements such as "It is like having a new brain," "I feel reborn psychologically," "I am on a higher plane of existence I never knew before," "I never knew one can experience such intense joy," and "I feel supernormal—if that is possible." Four of these 5 patients had bipolar family history.

The more noteworthy finding common to all responders is that they were now able to cope with ongoing stressors—even major ones—without decompensation. Thus, many patients stated that minor aggravations of daily existence, which used to overwhelm them, could now be dealt with easily. These responders no longer met Axis II diagnoses at the trait level. Over months to years prior to the institution of rigorous and appropriate pharmacotherapy, these patients had needed various forms of psychotherapy 6 or more times per month; following thymoleptic response, most of them were seen no more than 6 times per year, without the need for formal psychotherapy. None of the responders required hospitalization throughout the follow-up period.

Table 1. Final Outcome of Dysthymia With Various Pharmacologic Regimens

Outcome	N
Fluoxetine responders (N = 24)	
Fluoxetine only	14
+Levothyroxine	7
+Lithium	2
+Doxepin	1
Fluoxetine nonresponders (N = 10)	
Lost to follow-up	7
Lithium < 6 months	2
Fluoxetine < 6 months	1
Other responders (N = 8)	
Tricyclics	3
MAO inhibitors	2
Lithium	3

Suicidal behavior—reported by 10 patients with dysthymia (24%) at index evaluation—was not observed throughout the follow-up period. Eight of 10 who had engaged in past suicidal behavior were among the responders. All suicidal activity had been through overdose, of which half (5 of 10) had been serious (e.g., requiring admission to a critical care unit). In these 10 patients, the mean period from first suicide attempt to index treatment (55.8 months) and the period of follow-up with state-of-the-art treatment (61 months) were comparable, suggesting that such treatment may have played a crucial role in preventing suicidal behavior.

Poor response to fluoxetine in dysthymic patients was associated with substance abuse history (91% vs. 13%) (Fisher exact test, p < .0001), but not with bulimic features (27% vs. 13%), (Fisher exact test, p = .35).

Fluoxetine side effects, which were generally transient and did not result in discontinuation of treatment, included headaches (N = 5), insomnia (N = 4), weight gain (N = 4), nausea (N = 2), vivid dreams (N = 2), sweating (N = 4), decreased libido (N = 6), anorgasmia (N = 3), and oversedation (N = 1). However, 4 developed agitation in the early course of their treatment with fluoxetine, and all 4 were dropout nonresponders (Fisher exact test, p = .006).

Table 1 summarizes the outcome status of all patients with different pharmacologic regimens. Ultimately, among responders, 3 were on TCA monotherapy, 2 on MAOI monotherapy, and 3 on lithium monotherapy. For optimal clinical benefit, to raise their GAF scores > 70, nearly half of the fluoxetine responders needed augmentation with either levothyroxine (N = 7), lithium (N = 2), or doxepin (N = 1). That fluoxetine was the crucial factor in fluoxetine responders was supported by the fact that fluoxetine discontinuation led to clinical deterioration in every augmented patient. That the superior quality of response among fluoxetine responders was not due to thyroid augmentation can be observed in the fact that only 2 (29%) of 7 fluoxetine responders who were augmented

with thyroxine had GAF scores > 80, in contrast to 10 (71%) of 14 nonaugmented fluoxetine responders. Furthermore, as can be gleaned from cases 1, 2, and 3 (see below), thyroid augmentation had been previously used unsuccessfully during TCA trials. Regarding lithium augmentation with fluoxetine in 2 fluoxetine responders, such augmentation had earlier failed during a TCA trial. Finally, doxepin used in case 1 (see below) had proved ineffective as an antidepressant and benefited the patient only as a bedtime sedative for insomnia.

In the entire cohort, 10 were deemed fluoxetine nonresponders. Seven of them (4 males and 3 females) were lost to follow-up before their treatment with fluoxetine could be adjusted or enhanced. In 2 other male patients who failed fluoxetine, we substituted lithium, and both showed good response, but did not stay on lithium long enough to meet the preestablished criterion for 6 months of sustained response. They reported by telephone to be doing well, just like a third male who, after using fluoxetine for less than 6 months, seems to have gone into remission without further intervention. These 3 patients appear to have cycled out of an intermittent dysthymic illness of the "sub-bipolar" type previously described by us.[8,31] We conservatively considered them fluoxetine nonresponders because their remission is best regarded as spontaneous recovery. We submit that future relapse in these 3 patients might be prevented with continued lithium prophylaxis; actually, as described earlier, 3 males (2 TCA and 1 fluoxetine failures) did respond to *continued* lithium monotherapy in the present series.

Once optimal treatment was established for a given patient, occasional downward dips in GAF scores were reversed with the use of terminal sleep deprivation, phototherapy, sleep hygiene, and reduction in caffeine and alcohol intake. Of those few patients on long-term weekly psychotherapy in the present sample, none crossed the GAF threshold of response (> 70) until the institution of pharmacotherapy specifically tailored to the needs of each patient.

The overall response to all treatments is 32 (76%) of 42 dysthymic patients. Spontaneous recovery is an unlikely explanation in this responder group prospectively followed up for 62.13 ± 36.98 months, because nearly all patients attempted to discontinue their medication for weeks at a time during the first 2 years, to painfully learn (due to return of symptoms) that they could not do without it. Reinstitution of pharmacotherapy in all such instances resulted in return to a GAF level > 70.

Case Studies

The following vignettes provide descriptions of prototypic dysthymic patients and their course with various treatments.

Case 1. A 23-year-old single commercial artist presented for outpatient care with depression she described as "so bad I have had it every day of my life." She typically felt worse in the morning. She reported feelings of worthlessness and excessive guilt over past sexual experiences and complained of chronic headaches. She also had recent onset of weight loss and decreased energy, and had entertained the idea of overdose. She dated her depression to age 10, around the time when her mother died in a car accident. She was always critical of herself, a "worrier and a compulsive overachiever." She had sensitive ideas of reference and a chronic preoccupation with "the uselessness of living in this saturnine world." Both her mother and brother had received treatment for recurrent depression.

Full past trials on nomifensine, 2 secondary TCAs, 3 MAOIs, trazodone, as well as lithium and liothyronine augmentation, all had yielded disappointing results. She received individual dynamic psychotherapy as well as cognitive group therapy throughout this refractory period. Fluoxetine, 20 mg, increased to 40 mg/day after 6 weeks, resulted in significant progress that peaked at 6 months. Only then was she able to break off an abusive relationship with an older man with whom she had been living for the past 3 years, and moved out on her own. Later on, she took her medication irregularly and relapsed, with prompt improvement when in compliance again. She described her progress on fluoxetine as "ongoing major stresses no longer overwhelm me." She is enjoying her work and is seeking a greater circle of friends. Her follow-up GAF is a robust 85. This case illustrates that, despite 5 years of resistance to all available pharmacologic and psychotherapeutic approaches, this patient responded to fluoxetine: for the last 5 years she has taken 40 mg/day and is essentially free of depression.

Case 2. This 75-year-old, married, retired English teacher reported feelings of futility, recurrent thoughts of death, and a sense of being engulfed in gloom when she awakened in the morning. She said that, since age 9, "I have never known happiness, yet I can't think of any external cause." She remembered herself as always being pessimistic and guilt-prone; she also described herself as sensitive to criticism, avoiding intimate contacts. Her brother attempted to shoot himself at age 35. The patient first sought professional help at 40 years of age, because by then—after a few years of marriage—"I was convinced that the depression was me, yet I could not refrain from ascribing terrible things to my husband."

Formal psychoanalysis, conjugal therapy, and minor tranquilizers she was given off and on over the years did little to alleviate her fluctuating depression; at the peak of these depressions she lost all interest in hobbies and avoided all social contact except at work. Only fluoxetine, gradually increased to 40 mg/day, in combination with doxepin, 75 mg h.s. for sleep, led to significant improvement and broke off her long-term dependence on lorazepam. The patient is now being seen only in outpatient follow-up once every 2 months. She reports occasional

minor sleep disturbance. Her relationship with her husband has much improved; she no longer perceives him as an "insensitive bastard." She has thus maintained good response for $4^1/_2$ years, the only extended period of well-being she has known since age 9. Her GAF score throughout this period has been > 80. This case illustrates, among others, the futility of marital therapy in chronic depressives who are not receiving competent antidepressant treatments. This case also illustrates that, unlike certain characterologic problems that tend to attenuate with age, dysthymia can continue its unrelenting course well into later life.

Case 3. This 25-year-old single paralegal was referred by her minister because of "painful social avoidance." She also reported that she had been "unhappy and depressed for as long as I can remember." When she was a child, the family moved "constantly" because of her father's job; she had difficulties adjusting in school early on, felt awkward and self-conscious about her physical appearance, and was unable to make friends. Nothing in life had given her pleasure, and she carried out her job "mechanistically." She lacked confidence and felt that the future held nothing for her. Alcoholism, depression, suicide, and anorexia nervosa were present in her mother's family, while her father and a paternal uncle had extensive histories of alcohol abuse. The patient reported that one of her uncles had abused her sexually when she was 13.

Given imipramine, increased to 250 mg/day over 6 weeks, she overdosed without warning and had to be hospitalized. She failed full trials of trazodone, tranylcypromine, and isocarboxazid. Her relative best—but still suboptimal—response was to phenelzine, 30 mg b.i.d., which she tolerated except for marked weight gain; lithium and T_3 augmentation did not appreciably boost her response. Despite continued individual psychotherapy, she had made little progress after $2^1/_2$ years of outpatient treatment: she remained "full of anger"—many therapists described her as "borderline"—and abandoned treatment. When she returned 2 years later, we prescribed fluoxetine, 20 mg/day. Within 10 days the patient reported a marked change in her mood; she began to smile and felt confident for the first time in her life. She became involved in a community organization and, subsequently, ventured into an intimate relationship. She was able to set and follow through with personal and career goals for a better future. She has continued in follow-up every 3 months and is maintained on a dose of 20 mg/day of fluoxetine, which has kept her essentially asymptomatic over the past 6 years, at a GAF score of 81. This case illustrates the disappearance of avoidant traits once the dysthymia is brought under control; more remarkably, her object relations are no longer characterized by unpredictable anger.

Case 4. This 44-year-old ophthalmologist presented with a lifelong history of being somber, unenthusiastic, and anhedonic, always downgrading himself and his achievements and brooding about negative outcomes. He was referred by his wife because he "rarely showed emotions in intimate moments," shunned leisure activities, and was so preoccupied with unnecessary details that they never got to do anything together. He described "habitual gloom and an unrelaxed disposition," which were often accompanied by arousal and muscle tension, but which were not related to specific preoccupation with obsessive themes; nor was there evidence for specific compulsions. Family history was negative for mood disorders.

This patient was so concerned with side effects of antidepressants that he was reluctant to take them, nor was he willing to engage in psychotherapy. When fluoxetine became available, he could be persuaded to try it. He did not tolerate 20 mg for 2 weeks on account of insomnia, but when the dosage was reduced to 20 mg on alternate days, he gradually improved over a period of 2 months, was more relaxed, smiling more often, participating—albeit somewhat passively—in leisure activities, and being less closed emotionally and less rigid in daily chores. He took fluoxetine for nearly 2 years and felt freed from the grip of something that was "weighing me down and hindering spontaneity." His pretreatment GAF score of 61 had been boosted to 81 posttreatment. The anxious-obsessive traits did also improve, because arguably they were secondary to a long-standing depressive inhibition. However, this patient eventually stopped fluoxetine treatment, stating that he "felt abnormal being normal" and that "being burdened with cares and responsibility was natural" for him. At last follow-up 4 years after stopping fluoxetine, his GAF score was 65. In retrospect, this patient illustrates the pitfalls of rapid normalization of lifelong dysthymic traits of a more or less ego-syntonic nature, especially when the demand for change is externally imposed.

Case 5. This 48-year-old art professor sought help because of his "lonesome existence dedicated to contemplation and sleep." He had had 2 courses of psychoanalytic therapy for "feeling miserable and intermittently suicidal since age 7." He added that since then "existing has always required effort I never had."

Although he had written much acclaimed scholarly books and periodically appeared on TV educational programs, he felt his career had been "at best mediocre." He explained: "I am able to write because the little energy I have is totally invested in my work." As a consequence, he felt he had "no life left in me." However, he did admit to occasional intense sexual arousal for a few hours when "my brain vibrates with each heartbeat." Masturbation at such times was "intolerably pleasurable." The very few times he had intimate relations with women—as a result of being "seduced" by graduate students—he had experienced "passive orgasms" and had felt "disgusted" by his own behavior. (He denied ever engaging in homoerotic behavior or fantasies.) These women invariably "dumped me because they said I am not fun outside the classroom."

There was independent testimony that his classroom behavior was full of "scholarly vigor" and even occasional "wit," in contrast to his habitual lethargy and somber countenance. However, he did not meet formal criteria for hypomania, nor cyclothymia. He wondered why, unlike his "more cheerful, extraverted, superenergetic brother"—who was a "womanizer"—he had "inherited the dark side" of his manic-depressive father.

As the father had achieved moderate "stability" on lithium, this salt appeared like a rational choice. He has been successfully maintained on lithium, 900 mg/day (mean blood level = 0.7 mEq/L), over $4^1/_2$ years. Although he continues to report some degree of low self-esteem, the intensity of suffering, self-castigation, and suicidal preoccupation have essentially disappeared. Most importantly, he is now a more spontaneous person and has been able to forge what to this point has been an enduring relationship. His pretreatment GAF score of 61 has been boosted to 75 posttreatment. This vignette illustrates the subtle bipolar hints in a subgroup of dysthymics, indicating the prospect of lithium.[8,31]

DISCUSSION

The main limitation of the present study is that it is not based on double-blind procedures with extensive use of rating scales. However, systematic long-term outcome studies on consecutive case series in actual service settings are presently unavailable on chronic mood disorders. Previous naturalistic studies have demonstrated that most dysthymics fail to recover during follow-up ranging 1 to 5 years.[32] In chronic depressives who had responded acutely to imipramine and were followed naturalistically, good results were observed over 1 to 5 years in the few (11 [28%] of 39) who stayed on imipramine monotherapy.[33] Better results were obtained with desipramine in a 2-year maintenance continuation of acute responders[34]; this is in part testimony that better tolerated antidepressants yield superior results because of better compliance (that is why in our 1980 study[8] we had favored secondary TCAs). The present naturalistic study which, among others, addresses such pragmatic issues, extends the value of pharmacotherapy in dysthymia over an average of 5 years of follow-up. We discuss below aspects of the long-term clinical management of dysthymia that have not received adequate resolution in the controlled trials.

Response and Gender

In the present study, we utilized whatever was clinically deemed best for a given patient. The present response rate is more than doubled when compared with that reported in our 1980 short-term study[8] (76% vs. 33%). The success of fluoxetine in the female dysthymics seems to account largely for this improvement, especially since some patients had been refractory to all treatments (see case reports) and showed a turnaround with fluoxetine. One plausible explanation of the gender difference in fluoxetine response is that serotonin function might be more dysregulated in depressed females as compared to their male counterparts.[35] Interestingly, one previous report[36] found MAOIs to be better than TCAs in female major depressive patients. Although the numbers are too few for a definitive statement, lithium appears more useful in male dysthymics in the present clinical sample. It is difficult to presage what could have happened to the patients who were lost to follow-up if lithium or thyroxine had been given to them earlier in treatment. Noncompliance, associated with substance abuse, occurred in 3 males and 2 females. Nevertheless, in those patients who complied with pharmacotherapy, substance abuse was brought under control (suggesting that the latter could be considered as a form of self-medication for dysthymia).

Hypomanic Switches

In spite of the absence of mania or clear-cut hypomania, a dysthymic subgroup might nonetheless be related to bipolar disorder.[8,37–41] Mania appears more likely to complicate dysthymia identified in childhood.[39] Dysthymia clinically first identified in adult life will, by definition, lack mania and overt hypomanic symptoms; antidepressants, however, might unmask a hypomanic potential in adult dysthymia. The latter phenomenon was observed in 7 of 65 TCA-treated dysthymic patients in our original report[8] and was significantly related to positive bipolar family history.[31] Intense eutonia and other dramatic positive mental status changes—a shift from a depressive baseline to hyperthymia—that emerged abruptly in fluoxetine-treated dysthymics in the present study seem to signal a bipolar diathesis and warrant clinical vigilance. In most instances, there is a need to reduce antidepressant dosage, e.g., fluoxetine, 20 mg 2–3 times per week, or 10 mg daily. Such reduction in dosage—or discontinuation—is also relevant to the management of agitation from fluoxetine and suggests the need to consider lithium or other mood stabilizers.

The Question of Fluoxetine-Induced Personality Change

Much controversy surrounds whether fluoxetine induces permanent changes in personality. This depends on what is meant by "personality." Certainly, prior to treatment, many dysthymics are morose, lethargic, and nonassertive and cope poorly with stress. In view of the chronicity of dysthymia, such symptoms act like traits, most typically reflected by Axis II "cluster C" attributes; the good functioning brought about by fluoxetine in such cases is best described as removal of depressive pathology. Since this pathology is handicapping, its removal does not constitute "cosmetic pharmacology" as asserted by Kramer.[42] Andrews et al.[43] have recently reported that

SSRI treatment markedly reduces irritability, worrying, neuroticism, trait depression, and trait anxiety, while modestly increasing conscientiousness; as these authors remark, SSRI-treated patients, rather than becoming "careless," become "care-less." More provocatively, Ravindran et al.[44] have found that among SSRI responders, alleviation of dysthymia (and depression in general) is significantly correlated with improvement in psychological coping mechanisms, particularly reduced emotional coping and perception (of both frequency and intensity) of daily hassles, without associated increase in perception of uplifts. Likewise, among normal volunteers, Knutson et al.[45] found that paroxetine reduced hostility in tandem with a general decrease in negative affect without any changes in positive affect; at least one index of social affiliative behavior increased. The foregoing data are consistent with our results, where better coping with ongoing stressors was overall a more solid correlate of fluoxetine response than hyperbolic descriptions of superior psychic well-being. The latter shifts in dysthymia noted in our patients, we believe, depend less on fluoxetine and more on a bipolar familial-genetic diathesis (4 of 5 cases in the present series).

Reversal of Social Dysfunction

The high rate of history of major depressive episodes among dysthymic individuals is in accord with a growing literature[8,37,39] which indicates that most dysthymics—especially those seen in tertiary care settings—pursue a "double depressive" course.[3] In other words, the modal course of dysthymia is long-standing chronicity that encompasses major depressive episodes. The most remarkable finding in the present study is that 76% of patients who had been immersed in gloom over much of their lives were essentially rendered symptom-free and functioned at a good-to-superior level throughout an average follow-up period of 5 years. The complete elimination of suicidal behavior during this period is best explained by the near complete elimination of depressive morbidity, both major and subthreshold. It is also noteworthy that, contrary to a prevalent clinical stereotype, the presence of personality traits from the anxious cluster—and indeed that of depressive temperament—did not prevent such a robust response to pharmacotherapy. Actually, Ravindran et al.[46] have argued that the depressive temperament is a predictor of positive response to an SSRI. This suggests that the depressive temperament might represent a putative underlying neuropharmacologic dimension of dysthymia. These considerations generally cohere with evidence of marked improvement[47,48] of social functioning with antidysthymic pharmacotherapy. However, there are some dysthymic individuals who, upon treatment with an SSRI, have "difficulty adjusting to normality" (as illustrated in case 4). Since such individuals with long-standing dysthymia may experience forced normalization as egodystonic, such "normalization" should not be the goal of antidysthymic treatment. In these individuals, it might be desirable to implement more gradual dosing or opt for a less ambitious psychological endpoint. In theory, in these patients, one could resort to fine-tuning with dimensional psychopharmacotherapy, something that may nonetheless evade us in practice.

The Question of Psychotherapy

One of the main reasons dysthymic patients seek psychotherapy is that their depression, albeit low-grade, has existed for such a long time that they have difficulty coping with the most mundane of their daily chores. Our opening quote from Kraepelin[1] describes, in more eloquent words, the social handicaps of these patients. As in our first report,[8] we have found psychotherapeutic efforts—as monotherapy—disappointing in addressing these patients' deficient sense of competence. We further submit that, in dysthymia of such severity that began in childhood, available psychotherapies do not seem to go beyond developing a therapeutic alliance. Moreover, as evidenced by the present case series, traditional TCAs are only modestly helpful, even with expert "augmentation" by various strategies. It is when fluoxetine was introduced—with various adjuncts as needed—that many of the patients effected major positive change in their clinical status. More formal long-term studies with fluoxetine and other SSRIs are needed to replicate our open clinical findings and to clarify many unresolved issues. The question whether "depression-specific" psychotherapies (such as behavioral or interpersonal) can, without medication, fully remove dysthymic symptoms and restore a sense of competence in the milder cases seen in more general practice settings will await further research. An eloquent plea in this regard has been recently made by Markowitz.[49] On the other hand, Cooper[50] has pointed out that the psychotherapist—unaware of the constitutional basis of dysthymia—might collude with the patient's masochistic defenses, thereby maintaining rather than alleviating the patient's psychopathology. As patient 1 so eloquently stated, she was able to make active use of what she was exposed to in psychotherapy sessions only after her disabling dysthymic illness was brought under control with a specific thymoleptic medication; indeed, only then was she able to walk out of an abusive relationship. Likewise, marital harmony was not restored in patient 2 until chronic depressive symptoms were brought under control. We therefore suggest that, until proven otherwise, psychotherapy in dysthymia be used as an *adjunct* to pharmacotherapy. Nonetheless, as the vignettes we present attest to, the long-term management of dysthymia with pharmacotherapy is an art that requires not only broad clinical experience in pharmacotherapy, but also a thorough understanding of the interpersonal context of depression.[51]

Dysthymia as a Constitutional Substrate of Major Depression

Subthreshold affective symptomatology has been found to be as, if not more, disabling than major depressive illness.[4] Moreover, it represents powerful predictors of major depressive episodes on a prospective basis.[52] The clinical findings reported in this article invalidate the opinion of those who tend to conceptualize dysthymia as the "lesser" form of depressive disorders. Primary dysthymia as described herein emerges as an "endogenous" depression, which, rather than being confined to major episodes, is instead spread out over long spans of the lifetime in an intermittent or fluctuating course.[53] The anxious, social phobic, and avoidant features—noted on Axes I and II—seem to reflect sequelae of long-standing subthreshold depression. Skeptics[54] might argue that, had we included all patients who met the criteria for dysthymia, the case could have been made for a "neurotic" subtype or "anxious dysthymia" as well. The thrust of our effort in this article, however, was to characterize a core dysthymic group of patients in whom past course and presenting complaints were dominated by low-grade depressive suffering. Any other definition of dysthymia to us appears too broad to be clinically meaningful.

As originally formulated by Kraepelin,[1] such "primary" dysthymia—not arising in the course of another psychiatric disorder—can now be said to be one of the constitutional substrates from which major affective episodes erupt periodically.[53] Traditionally, prophylaxis in depressive illness has been aimed at the superimposed major episodes. The present findings not only demonstrate efficacy of long-term pharmacotherapy on the dysthymic—depressive temperamental—substrate of depressive illness, but also show the superior quality of adaptive functioning achieved in a high proportion of our patients. It is presently unknown whether this is due to some specificity of the serotonin system to the biological substrates of dysthymia.[46] Given the need for long-term treatment of dysthymia, the good tolerability and acceptance of SSRIs by patients might represent plausible reason for their success. It would appear that such or similar beliefs have led clinicians to treat the range of dysthymic pathology—previously deemed "refractory"—with greater enthusiasm and rigor.[55]

Implications for Public Health

At least 3% of the population suffers from dysthymia.[56] As in previous reports in the literature,[8,57,58] the present study found that at entry, dysthymic patients were grossly undertreated. Given the very high annual economic burden of depressive disorders (especially in their chronic forms),[59] the 7-fold reduction in hospitalization, the 12-fold reduction in ambulatory visits, and the suppression of suicidality should serve as an impetus for more formal studies to curtail the direct costs of treating the pernicious forms of this disease, which do not normalize between major episodes. Actually, a recent 12-year prospective study has shown that interepisodic dysthymia represents the most common symptomatic expression of major depressive illness (i.e., patients spend 27% of time in dysthymia compared with 15% in major depressive episodes).[60]

Drug names: desipramine (Norpramin and others), doxepin (Sinequan and others), fluoxetine (Prozac), levothyroxine (Synthroid and others), liothyronine (Cytomel), lorazepam (Ativan and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), tranylcypromine (Parnate), trazodone (Desyrel and others).

REFERENCES

1. Kraepelin E. Manic-Depressive Insanity and Paranoia. Robertson GM, ed; Barclay RM, trans. Edinburgh, Scotland: E & S Livingstone; 1921
2. Akiskal HS, Cassano GB. Dysthymia and the Spectrum of Chronic Depressions. New York, NY: Guilford; 1997
3. Keller MB. Dysthymia: course, outcome and impact on the community. Acta Psychiatr Scand 1994;89(suppl 383):24–34
4. Wells KB, Burnam A, Rogers W, et al. The course of depression in adult outpatients: results from the medical outcomes study. Arch Gen Psychiatry 1992;49:788–794
5. Howland RH. General health, health care utilization and medical comorbidity in dysthymia. Int J Psychiatr Med 1993;23:211–238
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition. Washington, DC: American Psychiatric Association; 1980
7. World Health Organization. International Classification of Diseases, Tenth Revision. Geneva, Switzerland: World Health Organization; 1992
8. Akiskal HS, Rosenthal TL, Haykal RF, et al. Characterological depressions: clinical and sleep EEG findings separating "subaffective dysthymia" from "character spectrum disorders." Arch Gen Psychiatry 1980;37:777–783
9. Kocsis JH, Frances AJ, Voss C, et al. Imipramine treatment for chronic depression. Arch Gen Psychiatry 1988;45:253–257
10. Stewart JW, McGrath PJ, Quitkin FM, et al. Chronic depression: response to placebo, imipramine, and phenelzine. J Clin Psychopharmacol 1993;13:391–396
11. Versiani M, Amrein R, Stable M. Moclobemide and imipramine in chronic depression (dysthymia). J Int Clin Psychopharmacol 1997;12:183–193
12. Lecrubier Y, Boyer P, Turjanski S, et al. Amisulpride versus imipramine and placebo in dysthymia and major depression. J Affect Disord 1997;43:95–103
13. Smeraldi E. Amisulpride versus fluoxetine in patients with dysthymia or major depression in partial remission: a double-blind, comparative study. J Affect Disord 1998;48:47–56
14. Hellerstein DI, Yanowitch P, Rosenthal I, et al. A randomized double-blind study of fluoxetine versus placebo in the treatment of dysthymia. Am J Psychiatry 1993;150:1169–1175
15. Vanelle JM, Attar-Levy D, Poirier MF, et al. Controlled efficacy study of fluoxetine in dysthymia. Br J Psychiatry 1997;170:345–351
16. Thase ME, Fava M, Halbreich U, et al. A placebo-controlled, randomized clinical trial comparing sertraline and imipramine for the treatment of dysthymia. Arch Gen Psychiatry 1996;53:777–784
17. Rush AJ, Koran LM, Keller MB, et al. Treatment of chronic depression, part 1: study design and rationale for evaluating the comparative efficacy of sertraline and imipramine as acute, crossover, continuation, and maintenance phase therapies. J Clin Psychiatry 1998;59:589–597
18. Keller MB, Gelenberg AJ, Hirschfeld RMA, et al. Treatment of chronic depression, part 2: a double-blind, randomized trial of sertraline and imipramine. J Clin Psychiatry 1998;59:598–607
19. Haykal RF. Is early onset dysthymia more treatable today? Proceedings of the American Psychiatric Association, Washington, DC; 1992 (Abstract #70E)
20. Akiskal HS, Bitar AH, Puzantian VR, et al. The nosological status of neurotic depression: a prospective three-to-four year examination in light of the primary-secondary and unipolar-bipolar dichotomies. Arch Gen Psychiatry 1978;35:756–766

21. Feighner JP, Robins E, Guze SB, et al. Diagnostic criteria for use in psychiatric research. Arch Gen Psychiatry 1972;25:57–63
22. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC: American Psychiatric Association; 1987
23. Akiskal HS. Dysthymic disorder: psychopathology of proposed chronic depressive subtypes. Am J Psychiatry 1983;140:11–20
24. Schneider K. Psychopathic Personalities. Hamilton MW, trans. Springfield, Ill: Charles C. Thomas; 1958
25. Klein DN. Depressive personality. J Abnorm Psychol 1990;99:412–421
26. Hirschfeld RMA. Major depression, dysthymia and depressive personality disorder. Br J Psychiatry Suppl 1994;65(suppl 26):23–30
27. Andreasen NC, Endicott J, Spitzer RL, et al. The family history method using diagnostic criteria: reliability and validity. Arch Gen Psychiatry 1977;34:1229–1235
28. Miller R. Simultaneous Statistical Inference. New York, NY: Springer-Verlag; 1988
29. Greden JF, Walters A. Caffeine. In: Lowinson JH, Ruiz P, Milman RB, eds. Substance Abuse: A Comprehensive Textbook. 2nd ed. Baltimore, Md: Williams & Wilkins; 1992:357–370
30. Extein I, Gold MS. Psychiatric applications of thyroid tests. J Clin Psychiatry 1986;47:13–16
31. Rosenthal TL, Akiskal HS, Scott-Strauss A, et al. Familial and developmental factors in characterologic depressions. J Affect Disord 1981;3: 183–192
32. Akiskal HS, Weise RE. The clinical spectrum of so-called "minor" depression. Am J Psychother 1992;46:9–22
33. Kocsis JH, Sutton BM, Frances AJ. Long-term follow-up of chronic depression treated with imipramine. J Clin Psychiatry 1991;52:56–59
34. Kocsis JH, Friedman RA, Markowitz JC, et al. Maintenance therapy for chronic depression. Arch Gen Psychiatry 1996;53:769–774
35. Lepage P, Steiner M. Gender and serotonergic dysregulation: implications for late luteal phase dysphoric disorder. In: Serotonin-Related Psychiatric Syndromes. Cassano GB, Akiskal HS, eds. London, England: Royal Society of Medicine; 1991:131–143
36. Davidson J, Pelton S. Forms of atypical depression and their response to antidepressant drugs. Psychiatry Res 1986;17:87–95
37. Klein DN, Taylor EB, Harding K, et al. Double depression and episodic major depression: demographic, clinical, familial, personality, and socioenvironmental characteristics and short-term outcome. Am J Psychiatry 1988;145:1226–1231
38. Rihmer Z. Dysthymia: a clinician's perspective. In: Dysthymic Disorder. Burton SW, Akiskal HS, eds. London, England: Gaskell, Royal College of Psychiatrists; 1990:112–125
39. Kovacs M, Akiskal HS, Gatsonis C, et al. Childhood-onset dysthymic disorder: clinical features and prospective naturalistic outcome. Arch Gen Psychiatry 1994;51:365–374
40. Angst J. Dysthymia and personality. Eur Psychiatry 1998;13:188–197
41. Cassano GB, Savino M. Chronic major depressive episode and dysthymia: comparison of demographic and clinical characteristics. Eur Psychiatry 1993;8:277–279
42. Kramer PD. Listening to Prozac. New York, NY: Viking Press; 1993
43. Andrews W, Parker G, Barrett E. The SSRI antidepressants: exploring their "other" possible properties. J Affect Disord 1998;49:141–144
44. Ravindran AV, Griffiths J, Waddell C, et al. Stressful life events and coping styles in relation to dysthymia and major depressive disorder: variations associated with alleviation of symptoms following pharmacotherapy. Prog Neuropsychopharmacol Biol Psychiatry 1995;19:637–653
45. Knutson B, Wolkowitz W, Cole SW, et al. Selective alteration of personality and social behavior by serotonergic intervention. Am J Psychiatry 1998;155:373–379
46. Ravindran AV, Bialik RJ, Lapierre YD. Therapeutic efficacy of specific serotonin reuptake inhibitors (SSRIs) in dysthymia. Can J Psychiatry 1994;39:21–26
47. Kocsis JH, Zisook S, Davidson J, et al. Double-blind comparison of sertraline, imipramine, and placebo in the treatment of dysthymia: psychosocial outcomes. Am J Psychiatry 1997;154:390–395
48. Miller IW, Keitner GI, Schatzberg AF, et al. Treatment of chronic depression, part 3: psychosocial functioning before and after treatment with sertraline or imipramine. J Clin Psychiatry 1998;59:608–619
49. Markowitz JC. Psychotherapy of dysthymia. Am J Psychiatry 1994;151: 1114–1121
50. Cooper AM. Will neurobiology influence psychoanalysis? Am J Psychiatry 1985;142:1395–1402
51. Schucter S, Downs N, Zisook S. Biologically Informed Psychotherapy for Depression. New York, NY: Guilford Press; 1996
52. Horwath E, Johnson J, Klerman GL, et al. Depressive symptoms as relative and attributable risk factors for first-onset major depression. Arch Gen Psychiatry 1992;49:817–823
53. Akiskal HS. Dysthymia as a temperamental variant of affective disorder. Eur Psychiatry 1996;11:117S–122S
54. Tyrer P, Seivewright N, Ferguson B, et al. The general neurotic syndrome: a coaxial diagnosis of anxiety, depression and personality disorder. Acta Psychiatr Scand 1992;85:201–206
55. Burton S, Akiskal HS, eds. Dysthymic Disorder. London, England: Royal College of Psychiatrists; 1990
56. Weissman MM, Leaf PJ, Bruce ML, et al. The epidemiology of dysthymia in five communities: rates, risks, comorbidity and treatment. Am J Psychiatry 1988;145:815–819
57. Weissman MM, Klerman GL. The chronic depressive in the community: unrecognized and poorly treated. Compr Psychiatry 1977;18:523–532
58. Shelton RC, Davidson J, Yonkers KA, et al. Undertreatment of dysthymia. J Clin Psychiatry 1997;58:59–65
59. Greenberg PE, Stiglin LE, Finkelstein SN, et al. Economic burden of depression in 1990. J Clin Psychiatry 1993;54:405–419
60. Judd LL, Akiskal HS, Maser JD, et al. A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. Arch Gen Psychiatry 1998;55:694–700