Persistent Depressive Disorder, Dysthymia, and Chronic Depression: Update on Diagnosis, Treatment

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An update on the diagnosis, causation, and treatment of chronic depressive problems. The focus is on the recently introduced diagnostic category of persistent depressive disorder.

Since the classic descriptions, depression has been conceived as an episodic and recurrent illness. Depressive episodes with clear onset and offset and sharp contrast with one’s usual mood and behaviors are perhaps the most conspicuous feature of severe mood disorders. However, systematic studies of unselected samples have been telling a different story: a large proportion of individuals suffer from low mood, lack of interest, and other symptoms of depression chronically, with some fluctuations but no clearly demarcated episodes. Chronic patterns of symptoms are often under-recognized and undertreated in the community.

This article provides an update on the diagnosis, causation, and treatment of chronic depressive problems, with a focus on the recently introduced diagnostic category of persistent depressive disorder (PDD).

Diagnosis
In DSM-III and DSM-IV, the protracted forms of depression have been conceptualized as dysthymia and by the chronic specifier of major depressive episodes. Dysthymia was characterized by milder symptoms not fully meeting criteria for MDD, but lasting 2 years or longer and meriting clinical attention because of the cumulative burden of long-standing symptoms. The symptomatic criteria for dysthymia differed in part from those for major depressive episode, with an emphasis on low self-esteem and hopelessness (Table 1).

In DSM-III and DSM-IV, dysthymia was trumped by MDD and was only diagnosed if the threshold for a major depressive episode was not met in the initial 2 years of symptoms. Major depressive episodes could be specified as chronic if the full criteria were continuously met for 2 years or longer. The validity of dysthymia and its separation from MDD has been repeatedly discussed and questioned. When individuals with dysthymia were followed over long periods, it became clear that most of them also developed major depressive episodes, which suggests that dysthymia and major depressive episodes are phases of the same disorder rather than separate conditions. Dysthymia and MDD also run in the same families and respond to the same treatments. On the other hand, both dysthymia and chronic depression are associated with more impairment, comorbidity, and suicide risk than less persistent forms of depression.

Chronic depression and dysthymia were merged into PDD in DSM-5. This new division of depressive disorders gives more weight to duration than to severity of symptoms. DSM-5 defines PDD on the basis of the set of symptoms for dysthymia, with the assumption that most individuals who meet the full symptoms for MDD also meet criteria for dysthymia. However, because of differences in symptomatic criteria, some individuals with chronic major depressive episodes will not meet the DSM-5 criteria for PDD.

While the merger of dysthymia and chronic depression into PDD is well justified by their strong sequential comorbidity and similar implications for prognosis and treatment, several aspects of the new diagnosis are not well supported by evidence and may not be useful. Why do we need 2 different sets of symptomatic criteria for MDD and PDD? The reliability and validity of the dysthymia criteria has not been formally tested, prompting concerns about the value of the new diagnosis. The assumption that most individuals with chronic depression also fulfill the dysthymia criteria may not hold consistently enough—it creates a group of individuals who suffer from chronic depression but do not receive the PDD diagnosis. While it is undisputable that prolonged duration and nonepisodic character are relevant, there is no good justification for the 2-year cutoff. In fact, some of the work used to justify the validity of persistent depression is based on a duration of 1 year or longer. For clinical and prognostic purposes, it is important to emphasize that duration of depressive
How common are the persistent forms of depression?
According to a large general population survey, 2.7% of Americans experience chronic MDD, 2.5% fulfill the diagnostic criteria for dysthymia, and 4.1% experience either chronic depression or dysthymia over their lifetime. Yet, only approximately 3.4% of Americans receive a lifetime diagnosis of DSM-5 PDD (Table 2). The difference between the intended definition of PDD (chronic depression or dysthymia) and the actual DSM-5 definition of PDD (dysthymia not trumped by MDD) is because approximately 1% of adults fulfill criteria for MDD with a chronic major depressive episode but do not meet the dysthymia criteria required for PDD. Because of the chronic nature and resulting impairment, persons who have persistent forms of depression are disproportionately represented among primary care and mental health service patients.

Causation
Since chronic forms of depression have typically been studied jointly with the episodic forms of depressive disorders, relatively less is known about the causation of PDD. However, existing data indicate partly overlapping and partly specific genetic and environmental factors. Persistent forms of depression run in families jointly with episodic recurrent depression. In addition to a general familial disposition to depressive disorders, there also appears to be a specific familial contribution to chronicity.

Familial disposition to dysthymia also overlaps with liability for personality disorders. Findings from a study of twins suggest that the overlap is due to genetic factors. One study of severe hospital-ascertained MDD in twins found that stronger heritability was associated with a greater number but shorter duration of episodes, which suggests that persistent depression might be less heritable than episodic depression. It is therefore likely that some of the familial aggregation of persistent forms of depression is due to environmental factors that are also shared within families. Environmental adversity is associated with depression in general and even more so with persistent depression. A history of childhood maltreatment, including physical abuse, sexual abuse, and emotional abuse and neglect, is especially strongly associated with persistent forms of depression. Regardless of treatment, patients with a history of childhood maltreatment were more likely to have a chronic course of illness. The long-term relationship between childhood maltreatment and perpetuation of depression into a chronic course appears to be strong, robust, and independent of environmental risk factors measured in adulthood.

The genetic and environmental factors that contribute to persistent depression are unlikely to be independent of each other. The short variants of the serotonin transporter gene promoter length polymorphism specifically sensitize individuals to develop chronic and persistent, but not transient or episodic, depression in adulthood following childhood exposure to maltreatment. This gene-environment interaction is perhaps the first example of a distinct causative mechanism specific to PDD. It remains to be established whether the knowledge of causation can inform and improve treatment.

Treatment of persistent depression
Many clinicians intuitively assumed that because of its long-standing nature and strong role of environmental factors, persistent depression may require a primarily psychological treatment, which may need to be different from that for episodic MDD. None of these assumptions have been borne out by evidence; antidepressants are at least as effective for PDD as for MDD, and psychological treatment designed specifically for PDD has not delivered consistent benefits.

The overall rate and degree of treatment success are lower in chronic depression than in non-chronic depression. For example, in the Genome-Based Therapeutic Drugs for Depression (GENDEP) study, individuals with a current chronic depressive episode improved less and had a lower probability of achieving remission than those with non-chronic depression, whether they were treated with escitalopram or with nortriptyline. However, because of a low placebo response, the relative benefit of antidepressant medication over placebo may actually be larger in PDD than in non-chronic depression.

A recent meta-analysis evaluated the efficacy and tolerability of treatments for persistent depression on the basis of direct and indirect comparisons and demonstrated that multiple compounds are effective for persistent depression. Drugs with strong efficacy and good tolerability included the antidepressants moclobemide (not approved for use in the US) and sertraline as well as the antipsychotic amisulpride (not licensed in the US or Canada). Imipramine also had strong efficacy supported by a large body of evidence, but it was less well tolerated. The large effect size of benefit from high-dose (mean, 675 mg/d) moclobemide and the results of a study showing that phenelzine...
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may outperform imipramine in chronic depression suggest that MAOIs may be an underutilized but effective option in the treatment of PDD.\textsuperscript{21,22} The finding that psychotherapy is less effective than medication for dysthymia may appear surprising and has to be qualified by more detailed analyses.\textsuperscript{23} It is important to note that the meta-analyses included no study of cognitive-behavioral therapy (CBT), the most extensively tested psychological treatment for depression. Most of the results were based on interpersonal therapy (IPT) and the cognitive behavioral analysis system of psychotherapy (CBASP).

IPT was significantly less effective than antidepressants and added only marginally significant benefits when combined with antidepressant treatment.\textsuperscript{21} CBASP was developed specifically to address the interpersonal patterns that presumably underlie the maintenance of chronic depression. In a large study, CBASP combined with the antidepressant nefazodone led to a response rate of 85%, a remarkable success in chronic depression.\textsuperscript{24} However, adding CBASP to antidepressants showed no significant benefit in a second, even larger study, in spite of intensive therapist training and adequate adherence to the CBASP protocol.\textsuperscript{25} The difference of CBASP performance in the two studies was so large that it has led to heterogeneity and statistically significant differences in a meta-analysis.\textsuperscript{21} Such inconsistent results suggest poor generalisability and the need to test the efficacy of treatments that have shown benefits across multiple studies. The obvious candidate is CBT.

Adding 12 sessions of individual CBT to antidepressants more than doubled response rates among patients with MDD resistant to antidepressants; 59% of the patients had a chronic depressive episode at baseline (and over three-quarters had depression lasting for a year or more).\textsuperscript{26} Another study showed the benefits of group CBT among chronically depressed patients with alcohol use disorder.\textsuperscript{27} These findings suggest that therapeutic effects of CBT will likely extend to persistent forms of depression. CBT for persistent depression should be explicitly evaluated.

Persistent depression will require a combination of antidepressant medication and high-quality, structured psychotherapy to achieve good long-term outcomes. A collaborative approach involving both a psychiatrist and clinical psychologist or CBT therapist in the care of the same patient is essential for delivery of effective treatment. One gap in evidence is the concurrent or sequential indication for medication and psychological treatment. In most research studies, the two treatments are started at the same time. This is unusual in clinical care.

The most common scenario in our specialized units for mood disorders is to first optimize pharmacotherapy (often with the use of MAOIs or augmentation of antidepressants) to achieve at least partial response and then start a course of CBT focusing on residual symptoms, individual maintaining factors (rumination, avoidance), and comorbid anxiety disorders. The case vignette provides an example to this approach. Future care may benefit from rigorous comparisons including sequential and stepped approaches to persistent depression.

**CASE VIGNETTE**

Caroline, a 50-year-old divorced mother of 2 adult children, is referred because of chronic depression, insomnia, and anxiety that has not responded to a number of antidepressants, augmentation attempts, and psychotherapy. During the assessment, she is tense, unable to relax, and anhedonic, with low energy and reduced affective reactivity. She states, “I have been depressed for 40 years.”

Her score is 24 on the Montgomery-Åsberg Depression Rating Scale (MADRS) and 35 on the Beck Depression Inventory (BDI). She meets DSM-5 criteria for PDD (with current major depressive episode), generalized anxiety disorder, and social anxiety disorder. She is currently taking 10 mg/d of escitalopram, 100 mg/d of lamotrigine, and 25 mg of quetiapine at bedtime. Titration of lamotrigine and quetiapine to therapeutic doses (250 mg and 200 mg, respectively) proves unsuccessful. Escitalopram is discontinued and after a washout period of 3 weeks, phenelzine is introduced and titrated to 15 mg 3 times daily (the last dose taken at 4 pm to reduce sleep problems and following dietary restrictions for MAOIs). After taking phenelzine for 8 weeks, Caroline has partial improvement (MADRS 14, BDI 23).

Caroline is assessed by a clinical psychologist and CBT is initiated, with a focus on activity scheduling, problem solving, and rumination. This is followed by a course of CBT for generalized anxiety disorder and for social anxiety disorder, including behavioral experiments and videofeedback (25 sessions total). After 8 months of treatment with phenelzine and CBT, Caroline’s depression (MADRS 5, BDI 9) and social anxiety symptoms remit. She is able to return to full-time employment and enjoy sports activities.

**Conclusion**
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Persistent Depressive Disorder, including previous categories of dysthymia and chronic depression, is associated with adverse prognostic indicators, including high rates of comorbidity, impairment, and suicide attempts. PDD can be effectively treated with antidepressant medication. Clinicians may want to consider MAOIs, at least in patients who do not respond to SSRIs. Adding structured psychological therapy, such as CBT, should be considered if remission is not achieved with medication.

Table 1: DSM-5 criteria for major depressive disorder and persistent d...

Table 2: Lifetime prevalence rates of persistent forms of depression i...

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Disclosures:

Dr Uher is Associate Professor and Canada Research Chair in the department of psychiatry at Dalhousie University in Halifax, Nova Scotia. He reports no conflicts on interest concerning the subject matter of this article.

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