REVIEW

Rational Treatment Choices for Non-major Depressions in Primary Care

An Evidence-based Review

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OBJECTIVE: **This review synthesizes available evidence for managing clinically significant dysphoric symptoms encountered in primary care, when formal criteria for major depression or dysthymia are not met. Discussion is focused on premenstrual dysphoric disorder (PMDD) and minor depression because of their significant prevalence in the primary care setting and the lack of clear practice guidelines for addressing each illness.**

DESIGN: **English language literature from prior systematic reviews was supplemented by searching MEDLINE, EMBASE, the Cochrane Controlled Trials Registry, the Agency for Healthcare Research and Quality National Guideline Clearinghouse, and bibliographies of selected papers. Studies addressing the natural history or treatment of minor depression or PMDD were selected for review. Data were abstracted by 1 of 2 independent reviewers and studies were synthesized qualitatively.**

RESULTS: **Five individual studies that compared antidepressant or psychological treatments to placebo in patients with minor depression suggest short-term improvements in depressive symptoms with paroxetine, problem-solving therapy, and cognitive behavioral therapy, but not with amitryptiline. Modest benefits on mental health function were reported with paroxetine and with problem-solving therapy, but only in patients with severe functional impairment at baseline. Twenty-four controlled trials were identified that compared antidepressant or psychological treatments to placebo in patients with premenstrual dysphoric disorder. Pooled results from a recent systematic review of 15 randomized controlled trials and one additional trial abstract provide strong evidence for a significantly greater improvement in physical and psychological symptoms with serotonin-selective reuptake inhibitor medications when compared with placebo. Individual trials also suggest significantly greater improvements in symptom scores with venlafaxine, but not with tricyclic antidepressants.**

CONCLUSIONS: **The limited evidence base for minor depression provides only mixed support for a small to moderate benefit for few antidepressant medications and psychological treatments tested. For the treatment of severe psychological or physical symptoms causing functional impairment in patients with PMDD, sertraline and fluoxetine are clearly beneficial in carefully selected patients.**

KEY WORDS: **depression; depressive disorder; premenstrual syndrome; antidepressive agents; psychotherapy; complementary therapies.**
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Major depression and dysthymia are prevalent in primary care, cause marked personal suffering, and are associated with increased mortality.[1] Antidepressant medications and depression-specific psychological treatments are clearly effective for major depression, and antidepressant medications benefit patients with dysthymia.[1–3] However, less severe depressive illnesses predominate in primary care settings.[4,5] Although 10% to 40% of primary care patients have significant depressive symptoms, less than half of them meet criteria for major depression as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).[6] Studies using formal criteria, such as DSM-IV, find that the prevalence of less severe depression ("minor" depression) is roughly twice that of major depression.[4,5,7] Observational studies show that these illnesses are associated with significant functional impairment.[8–10] These "minor depressions" are not so minor.

Survey data suggest that primary care physicians make few treatment distinctions between major and less severe depressions.[11] Most are treated with antidepressants, contributing to the rapid rise in antidepressant drug costs. Given that these treatments are costly and may have adverse effects, it is appropriate to evaluate whether treatment is beneficial and if the benefits outweigh adverse effects. This evidence-based review will briefly summarize the diagnosis, natural history, and treatment trials for 2 common, non-major depressions.

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DEFINING CLINICAL DEPRESSIVE CONDITIONS

Clinical depression is a syndromal diagnosis, based on the presence of a group of associated depressive symptoms and the exclusion of competing diagnoses. Depressive symptoms are generally evaluated along 3 continuums: intensity, duration, and degree of impact on daily functioning. Using these elements, symptoms can range from simple dysphoria, lasting only hours or a few days, to major depression, characterized by multiple symptoms and substantial impact on daily functioning (Table 1).[12] A diagnostic nomenclature adopted by the American Psychiatric Association—major depression, dysthymia, and depression not otherwise specified (NOS)—is depicted in the DSM-IV and can help to guide treatment. Major depression is defined by depressed mood or loss of interest in nearly all activities for at least 2 weeks, accompanied by a minimum of 3 to 4 (for a total of 5) additional psychological and somatic symptoms.[12] Dysthymia is characterized by fewer symptoms than major depression (less than 5) and a chronic course (lasting at least 2 years). Depression NOS includes syndromes without sufficient number of symptoms (less than 5) or duration (less than 2 weeks) to meet major depression criteria (Table 1). Although disorders categorized as depression NOS fail to meet specific diagnostic requirements for major depression or dysthymia, they by definition still cause "clinically significant distress or impairment in social, occupational, or other important areas of functioning."[7,12]

Depressive states not meeting major depression criteria for *number* of symptoms (i.e., ≥5), and not meeting duration criteria for dysthymia (i.e., >2 yrs) have come to be known as "minor," "subthreshold," or "subsyndromal" depression.[3] Although these disorders can be further defined by the pattern of recurrence, and specific symptomatology, there is not widespread agreement on further subcategorization. For simplicity, we refer to them collectively as "minor" depression. Additionally, DSM-IV classification of minor depression requires the absence of a prior major depressive episode. Numerous patients presenting with subthreshold dysphoric symptoms in general practice fall into this latter category, but would be better categorized as "major depression in partial remission." The most clinically prominent example of depressive states not meeting formal diagnostic criteria for symptom *duration* is premenstrual dysphoric disorder (PMDD). Because PMDD is specific to women and is uniquely associated with particular physical as well as psychological symptoms (Table 2), we will address it separately from minor depression. In the absence of clear practice guidelines for addressing PMDD and minor depression, this review will focus on the existing evidence base for treatment choices in patients with these disorders.

METHODS

The Cochrane Database of Systematic Reviews was searched for applicable systematic reviews. Identified reviews were supplemented by searches of the electronic databases MEDLINE (1/1966–2/2001), EMBASE (1/1988–8/2000), and the Cochrane Controlled Trials Registry, using the terms "premenstrual syndrome," "premenstrual dysphoric disorder," or "late luteal phase dysphoric disorder,'' and separately, ''depressive disorder,'' or "depression," and "minor," "subsyndromal," "subthreshold," or "nonmajor." Bibliographies of selected papers were reviewed for additional studies. The Agency for Healthcare Research and Quality National Guideline Clearinghouse was searched for relevant clinical guidelines. Studies addressing the natural history or treatment of minor depression or PMDD were selected for review. Data were abstracted by 1 of 2 independent reviewers and study outcomes were synthesized qualitatively.

Table 1. Diagnostic Nomenclature for Clinical Depressive Conditions

DSM-IV	Diagnostic Criteria	Duration
Major depression	≥5 depressive symptoms* (must include either depressed mood or anhedonia)	≥2 weeks
Dysthymia	3 or 4 dysthymic symptoms†, (must include depressed mood)	≥2 years
Depression NOS	Variable; all included disorders must cause clinical significant impairment of daily functioning but fail to meet classification for major depression or dysthymia. Examples include:	Variable
	minor depression‡: 2 to 4 depressive symptoms*	≥2 weeks
	premenstrual dysphoric disorder (PMDD):	<2 weeks
	Intensity may be comparable to major depression, regularly occuring during the last week of the luteal phase and remitting within a few days of the onset of menses, and recurring during most menstrual cycles over the preceding 12 months.	

* *Depressive symptoms are depressed mood, loss of interest in most activities (anhedonia), significant change in weight or appetite, insomnia or hypersomnia, decreased concentration, decreased energy, inappropriate guilt or feelings of worthlessness, psychomotor agitation or retardation, and suicidal ideation.*

† *Dysthymic symptoms are generally the same as depressive symptoms, with the addition of feelings of hopelessness and the omission of suicidal ideation.*

‡ *Additional closely related terms, such as subthreshold depression and subsyndromal depression, are not further distinguished here, and for purposes of simplicity, will be collectively referred to in the text as minor depression.*

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; NOS, not otherwise specified.

Table 2. Diagnostic Classification of Premenstrual Dysphoric Disorder (PMDD)*

Psychological symptoms
Markedly depressed mood†
Marked anxiety or feeling "on edge"†
Suddenly sad/tearful or increased sensitivity to refection†
Marked irritability or anger or increased interpersonal conflicts†
Significant change in weight or appetite
Insomnia or hypersomnia
Decreased concentration
Decreased energy
Loss of interest or pleasure in activities (anhedonia)
Sense of being overwhelmed or out of control
Somatic symptoms
Breast tenderness, headache, myalgias, arthralgias, or sense of "bloating"

** Diagnosis requires the presence of ≥5 of 11 possible symptoms (10 psychological 1 somatic). Symptoms regularly occur during the last week of the luteal phase and remit within a few days of the onset of menses. Distinction is made from more common "premenstrual syndrome" (PMS) by the number of symptoms and presence of significant interference with occupational or social functioning.*

† At least 1 of these 4 cardinal symptoms must be experienced during most menstrual cycles over the preceding 12 months.

We reviewed treatments evaluated in randomized controlled trials including antidepressants, psychological treatments, and complementary treatments. Specific types of structured psychological therapies (as administered by trained mental health specialists) that are considered here include problem-solving therapy and cognitive and behavioral therapy. Cognitive behavioral therapy (CBT) involves identification and confrontation of thoughts that perpetuate depression ("cognitive") and a conscious effort to decrease behaviors that reinforce depression while engaging in more positive and productive activities ("behavioral").[13] Problem-solving therapy involves training patients to approach tasks that feel insurmountable by conceptualizing and approaching them as several smaller, more manageable problems.[14]

Reported results from systematic reviews are presented in terms of relative response rates in the treated compared to the control group, where response is defined as achieving clinically significant symptom reduction as measured by various depressive or premenstrual syndrome (PMS) symptoms scales. Studies evaluating antidepressant treatments for minor depression were not analyzed quantitatively because of heterogeneity in study design and outcome measures.

RESULTS

Natural History of Minor Depression and PMDD

Because of variability in diagnostic criteria and the relatively recent interest in these conditions, their natural history is not well described. Epidemiological studies focusing on general practice patients with minor depression show that approximately 8% have persistent subthreshold symptoms, and 10% to 18% develop major depression at 1 year.[8,9,15] At 2 years of follow-up, 7% continue to have symptoms, thereby meeting diagnostic criteria for dysthymia.[5] Prospective cohort studies show that the presence of the symptom of depressed mood (relative risk [RR] 1.6 to 5.4) or the presence of 4 or more total symptoms when depressed mood is absent (RR 8.2 to 47.3) is associated with an increased risk for the development of major depression or dysthymia.[5] Furthermore, at 1 year of follow-up, approximately 20% of minor depressive patients are estimated to have moderate to severe social disability.[8–10] The definition of these syndromes as "minor," therefore, clearly does not imply minimal risk for adverse clinical outcomes.

Because it is a recurrent disorder, occurring exclusively in female patients, PMDD requires separate attention. This disorder is defined by regularly recurrent physical and psychological symptoms that occur only in association with the luteal phase of the reproductive cycle (Table 2).[16,17] PMDD is differentiated from more common premenstrual physical and mood symptoms that are experienced to some degree by most women (premenstural syndrome) by its increased severity and significant impairment in social or occupational function.[18] Although this disorder has at times been minimized because symptom duration is short (<2 weeks), the symptom severity and functional impairment is often significantly severe. The mean age of onset is approximately 26 years, and the disorder has been estimated to afflict 2% to 9% of women of reproductive age.[1,16] Long-term prognosis may be complicated by an inordinately high lifetime prevalence of major depression or an anxiety disorder.[19] Because PMDD is recurrent in nature, there is potential for substantial cumulative morbidity over the course of an individual's lifetime. Little more is known about the natural history of this disorder and its relationship to other depressive states.

TREATMENTS

Antidepressants and Psychological Treatments for Minor Depression

The evidence base for minor depression is limited; no formal literature synthesis has been reported. Only 5 studies compared an antidepressant or psychological treatment to placebo (Table 3). In a subgroup analysis with limited power, amitryptiline at a median dose of 125 mg/day was no more effective than placebo in 37 general practice patients.[20] Minaprine, an antidepressant drug with actions on multiple neurotransmitters but unavailable in the United States, showed small but significant effects in older patients with "prolonged depressive reaction."[21] A trial evaluating both paroxetine and problem-solving therapy administered in a primary care setting showed mixed effects for 204 primary care patients aged ≥60 with at least 4 weeks of depressive symptoms.[22] Compared to placebo, paroxetine improved depressive symptoms modestly, but

Table 3. Major Characteristics of Controlled Trials in Patients with Minor Depressive Conditions

First Author	Sample Size*	Setting	Comparison	Duration	Major Qualitative Result(s)
Paykel[20]	37	Primary care	Amitriptyline 125 mg/day vs placebo	6 wk	No significant improvement in depressive symptoms
Parnetti[21]	130	Not clearly stated	Minaprine vs placebo	12 wk	Small, statistically significant improvement globally and in depressive symptoms compared to placebo
Williams[22]	204	Primary care	Paroxetine 10–40 mg/day vs problem-solving therapy vs placebo	11 wk	Modest, statistically significant improvement in depressive symptoms for paroxetine and problem-solving therapy compared to placebo Functioning improved clinically significantly for paroxetine and problem-solving therapy groups, but only when severe functional impairment was present at baseline
Miranda[23]	49	Primary care	Cognitive behavioral therapy vs no intervention	8 two-hr sessions	No significant effect on depressive symptoms after completion of CBT, but moderately positive effect when compared with placebo group at 4- and 12-mo follow-up
Lynch[24]	29	Primary care	Telephone-administered PST vs no intervention	6 sessions	Trend toward improvement in depressive symptoms scores but statistically insignificant at conclusion of intervention

** Number of patients with minor depression, which for some studies is a subset of the total sample.*
CBT, cognitive behavioral therapy; PST, problem-solving therapy.

mental health functioning, using the SF-36 scale, improved clinically significantly only for patients with the most severe functional impairment at baseline. Problem-solving therapy resulted in a modest, delayed benefit on depressive symptoms and, like paroxetine, improved function only in those with the most impairment at baseline. In addition, 2 trials evaluated psychosocial interventions. In a controlled trial, Miranda and Munoz evaluated 8 sessions of CBT in an ethnically diverse, urban, primary care population. At 4 months' postintervention, CBT showed a delayed, moderately positive effect that persisted to the 12-month follow-up.[23] An underpowered trial in family practice showed positive but statistically insignificant effects of a telephone-based problem-solving therapy.[24]

Two studies comparing multifaceted interventions (including pharmacotherapy) to usual primary care for depression showed important positive effects for the subgroup with major depression but not for minor depression.[25,26] Although the proportion of patients receiving at least 3 months of adequate antidepressant medication increased from about 40% to almost 80%, patients with minor depression were not benefited. Both the multimodal intervention and usual-care treatments produced very high response rates for patients with minor depression (50% to 70%). Collectively, these studies provide only mixed support for a small to moderate benefit for the antidepressant medications and psychological treatments tested. Applying these results in clinical practice is complicated by definitions for minor depression that varied in every study reviewed.

Antidepressants and Psychological Treatments for Premenstrual Dysphoric Disorder

A recently published systematic review of selective serotonin reuptake inhibitor (SSRI) therapy for women with severe PMS symptoms (PMDD) included a meta-analysis of treatment outcomes from 15 well-designed randomized-controlled trials involving 904 women.[17] We identified 1 additional trial abstract[27] evaluating treatment with an SSRI, as well as 8 additional controlled trials investigating various active treatments other than SSRIs.[28–35] Major characteristics and qualitative results from these trials are summarized in Table 4. Trials were conducted almost exclusively in university settings, with patients recruited by advertisement, referral, or through a specialized premenstrual syndrome clinic. Patients were carefully screened to ensure that diagnostic criteria were met and to exclude patients with recent or ongoing major depression or coexisting psychiatric illness such as alcohol abuse. Treatments evaluated by individual trials included sertraline, fluoxetine, paroxetine, fluvoxamine, citalopram, clomipramine, venlafaxine, maprotoline, desipramine, bupropion, alprazolam, atenolol, and bright-light therapy.

Table 4. Major Characteristics of Controlled Trials in Women with Premenstrual Dysphoric Disorder (PMDD)

Category of Intervention	First Author	Sample Size	Setting	Intervention and Control	Duration	Major Qualitative Result(s)
SSRI therapy	Dimmock[17] (synthesis of 15 RCTs)	904 Total (15 trials) 364 Sertraline (5 studies) 398 Fluoxetine (7 studies) 69 Citalopram (1 study) 53 Paroxetine (1 study) 20 Fluvoxamine (1 study)	Primarily university settings or specialty PMDD clinics	Variable dosage 11 trials continuous daily dosing 4 trials luteal phase only dosing	Majority of included trials were 2–3 menstrual cycles in duration	Statistically and clinically significant improvement in psychological and physical symptoms for active treatment
	Halbreich[27]	281	Unclear	Sertraline 50–100 mg/d (luteal phase only) vs placebo	3 menstrual cycles	Statistically significant improvement in premenstrual symptoms when compared with placebo
Non-SSRI pharmacotherapy	Freeman[28]	157	Unclear	Venlafaxine 50–200 mg/d (continuous) vs placebo	4 menstrual cycles	Statistically and clinically significant improvement in depressive symptoms compared with placebo
	Freeman[28]	168	University	Progesterone (intravaginal), 400–800 mg/d (luteal phase only) vs placebo	2 menstrual cycles	No difference in depressive symptoms compared with placebo
	Rausch[30]	16	Unclear	Atenolol, 50 mg/day (luteal)	1 menstrual cycle	No significant improvement in symptom rating scales when compared with placebo
	Sundblad[31]	40	Unclear	Clomipramine 25–75 mg/d (continuous) vs placebo	3 menstrual cycles	Statistically and clinically significant improvement in daily symptom rating scales and global improvement rating when compared with placebo
	Sundblad[32]	29	Unclear	Clomipramine 25–75 mg/d (luteal phase only) vs placebo	3 menstrual cycles	Statistically and clinically significant improvement in daily symptom rating scales and global improvement rating when compared with placebo
	Harrison[33]	30	Unclear	Alprazolam 1–4 mg/d (luteal) vs placebo	3 menstrual cycles	Statistically significant improvement in daily symptom rating scales and global improvement rating when compared with placebo
	Berger[34]	48	Unclear	Alprazolam 0.5–3 mg/d (continuous) vs placebo	3 menstrual cycles	Statistically significant improvement in primarily anxiety cluster symptoms on daily symptom rating scales when compared with placebo
Bright-light therapy	Lam[29]	14	Unclear	Cool-white fluorescent light 30 min/d (luteal phase only) vs placebo (red fluorescent light)	2 menstrual cycles	"Significant improvement" in prospective luteal phase symptom scores when compared to placebo

SSRI, serotonin selective reuptake inhibitors; RCT, randomized controlled trial.

The majority of trials (96%) studied short-term (≤3 to 4 months) interventions and generally did not report any long-range follow-up beyond the intervention period.

No controlled trials of psychological treatments were identified for PMDD, but at least 5 trials evaluated CBT for premenstrual syndrome. These trials are relevant because they included some patients with "severe premenstrual syndrome" and dysphoria.[36–40]

The systematic review by Dimmock and Wyatt concluded that SSRI therapy is associated with a 6.9-fold (95% confidence interval, 3.9 to 12.2) greater improvement in physical and psychological symptoms, as assessed by various prospective symptom-based rating scales, when compared to placebo. The best-studied treatments are sertraline (5 studies, 364 subjects) and fluoxetine (7 studies, 398 subjects); citalopram, fluvoxamine, and paroxetine have been evaluated in single trials. Limited trial data and differences in study treatment regimens made it impractical to evaluate for differences in effectiveness among different SSRIs or different dosages of the same SSRI. Although 13 of 15 trials enrolled patients based primarily on psychological symptoms of PMDD, there appeared to be a comparable response in decline of physical symptoms. Four of the 15 trials used intermittent or semi-intermittent dosing regimens. Sensitivity analyses with these individual groups showed that intermittent regimens were also significantly more effective than placebo and comparable in effect to continuous dosing regimens. A recently reported trial of 281 women with PMDD, not included in this systematic review, reported significant improvements in global clinical assessments in those treated with luteal-phase sertraline therapy when compared to placebo.[27]

Support for alternatives to SSRI pharmacotherapy comes from an abstract reporting a significantly greater improvement in daily symptom scores in 157 women with PMDD who were treated with 50 to 200 mg of venlafaxine daily, when compared with placebo.[35] There are limited data from small studies suggesting potential benefit for alprazolam, atenolol, bright-light therapy, and the primarily *serotonergic* tricyclic antidepressant clomipramine.[28–34] Two randomized trials evaluating the primarily *noradrenergic* tricyclic antidepressants maprotiline and desipramine, however, failed to show significant treatment benefits when compared to either placebo or an SSRI.[41,42] Evidence for CBT is mixed for premenstrual syndrome; 3 trials show benefit[36–38] while 2 trials show no benefit over placebo.[39,40] It is unclear how these results would translate to patients with PMDD. We did not identify trial data for other psychological treatments.

Although antidepressant medications showed benefit in patients with PMDD, translating these results to routine clinical practice may be challenging. First, patients were highly selected and may not be typical of patients with PMDD in primary care. Second, most trials used placebo run-in or symptom monitoring phases to exclude placebo responders and subjects who would not adhere to the protocol. For these reasons, effectiveness in routine clinical practice may be less than that seen in these trials.

Herbals and Other Treatments

A wide range of herbal and other complementary treatments have been evaluated for major depression or premenstrual syndrome. Although these therapies have not been evaluated specifically in patients with minor depression or PMDD, we review selected treatments because patients and their physicians frequently consider them.

Two recent literature syntheses evaluated herbal treatments for depressive disorders.[2,43] St. John's Wort (hypericum) was evaluated in 17 placebo control trials; there were no studies evaluating the herbals Kava Kava or Valeriana. St. John's Wort was more effective than placebo at achieving clinically significant symptom reduction as measured by various depressive symptoms scales (relative response rate 2.47; 95% confidence interval, 1.69 to 3.61) in patient populations consisting predominately of individuals with major depression or dysthymia, but including some with adjustment disorder.[43] A recent randomized trial studying patients in tertiary care clinics with predominantly recurrent major depression averaging greater than 2 years in duration found that St. John's Wort was not superior to placebo.[44] It is unclear how these results would translate to patients with minor depression or PMDD. Further, commonly available preparations of St. John's Wort may not meet the standards followed in these trials for active ingredients.

Aerobic exercise, typically in at least 3 supervised sessions per week, has been effective in controlled studies for mild to moderate major depression and for premenstrual syndrome.[45–51] There is limited trial evidence that vitamin B6, and evening primrose oil may benefit premenstrual syndrome. In 5 poor-quality trials reporting effects on depressive symptoms, patients taking Vitamin B6 (50 to 600 mg/day), were 1.69 (95% confidence interval, 1.39 to 2.06) times more likely to improve than those taking placebo.[49] Of the 6 small studies reporting the effects of evening primrose oil, only 3 showed small beneficial effects overall.[52] It is unclear if similar results would be obtained in patients meeting the stricter criteria for PMDD.

Adverse Effects

A recent systematic review compared common adverse effects for SSRIs versus tricyclic antidepressants in patients with major depression.[2] Although adverse event rates for patients with minor depression may differ from those with major depression, these data are the most direct evidence available until more treatment studies are completed in patients with minor depression. In major depressive patients, headache (15% vs 11%), insomnia (13% vs 6%), and diarrhea (12% vs 3%) were significantly more common for SSRIs. Dry mouth (48% vs 18%),

constipation (21% vs 8%), dizziness (19% vs 8%), tremors (11% vs 7%), blurred vision (10% vs 6%), and urinary disturbances (8% vs 3%) were more common for tricyclic antidepressants.[2] Primary care patients treated with tricyclic antidepressants were more likely to discontinue treatment due to an adverse effect (13%) than were patients treated with a newer agent (8%) and were more likely to change to a different class of antidepressants than were patients begun on an SSRI.[53] Adverse effects on sexual function, a relatively frequent adverse effect of SSRIs, could not be evaluated quantitatively. In patients with severe PMS/PMDD, treatment with an SSRI is associated with significantly higher adverse effects than placebo treatment.[17] The most common complaints were insomnia, gastrointestinal irritability, and fatigue. Adverse effects serious enough to lead to treatment dropout were seen predominantly in a single study using 60 mg of fluoxetine daily.[17]

Serious or life-threatening adverse effects occur in less than 1% of patients taking newer antidepressants.[43] Serious adverse effects associated with serotonin reuptake inhibitors are bradycardia, bleeding, granulocytopenia, seizures, hyponatremia, hepatotoxicity, serotonin syndrome, extrapyramidal effects, and mania in unipolar depression. Buproprion is associated with seizures. Tricyclic antidepressants are more likely than serotonin reuptake inhibitors to be lethal when taken in overdose.[1] Vitamin B6 is associated with peripheral neuropathy at doses exceeding 200 mg/day.[54] Clinically important drug interactions occur with all classes of antidepressants. Recently, important drug interactions have been described between protease inhibitors, some immunosuppressants, and hypericum.[55] Finally, abrupt discontinuation of prescription antidepressants can cause gastrointestinal or somatic distress, sleep disturbances, mood fluctuations, and movement disorders.[56] These withdrawal syndromes appear in proportion to the daily dosage and length of treatment and are more common with short-half-life drugs.

DISCUSSION

Areas of Uncertainty

There are considerable areas of uncertainty regarding almost all aspects of minor depression and PMDD. The most pressing needs are for better studies of the natural history and validated clinical predictors of poor outcome. For minor depression, the limited trial data do not offer definitive guidance on treatment options. Psychological treatments, which seem particularly appropriate for these milder depressions, need better evaluation. In major depression, continuing effective antidepressant treatment for at least 6 months after the initial response decreases the risk of relapse by 70%.[2] We need similar longitudinal trial data for minor depression and PMDD to guide decisions regarding optimal treatment duration and to predict long-term treatment efficacy. Finally, longer-duration trials will help to identify whether witnessed short-term benefits are lasting and whether longer-duration therapy is associated with additional adverse effects.

Status of Current Practice Guidelines for Minor Depression and PMDD

Currently, there are no treatment guidelines for minor depression or PMDD. Both the Agency for Healthcare Research and Quality and the American Psychiatric Association have published guidelines for the diagnosis and treatment of major depressive disorder.[3,57] These guidelines acknowledge the clinical relevance of minor depression and PMDD and a need for further research, but do not offer treatment recommendations. A 1997 guideline for depressive disorders in women, published by the Association of Professors of Gynecology and Obstetrics, focuses primarily on treatments for major depressive disorder.[16] This guideline emphasizes the significant contribution of PMDD to female morbidity, but it does not revisit the disorder in its algorithm for treating depressive disorders. The most recent guideline for pharmacological treatments of acute major depression and dysthymia, published by the American College of Physicians – American Society of Internal Medicine (ACP-ASIM), is based on a systematic review of newer pharmacotherapies for depression.[58] Although the guideline does not specifically address minor depression, the systematic review states: "There is insufficient evidence to establish whether newer antidepressants are effective for subsyndromal (minor) depression. . . ."[2]

Author Recommendations

- When initially evaluating patients with depressive symptoms, it is imperative that primary physicians carefully assess the number and duration of depressive symptoms and degree of functional impairment. This will distinguish patients with severe impairment and numerous persistent symptoms (i.e., major depression), or those experiencing lesser symptoms but of chronic duration (i.e., dysthymia), from those with less well-identified but clinically significant and prevalent states such as minor depression and PMDD.
- Referral to a skilled psychiatric consultant should be immediately considered in those patients exhibiting suicidal ideation, or manic or psychotic symptoms.
- For depressed patients with clinically significant social or occupational functional impairment, but not meeting threshold diagnostic criteria for major depression or dysthymia or having a history of major depressive illness (i.e., patients with minor depression), current data suggest that clinicians should consider active treatment only for those with more severe functional impairment; a 4- to 8-week trial of support, education, and when appropriate,

exercise should be considered for all others. Patients should be re-evaluated, probably in several face-to-face contacts, before concluding either that the depression is resolved or that there is a need for further intervention. For individuals who worsen or have persistent symptoms and increasing functional impairment, a trial of antidepressant medication or referral to a skilled psychotherapist for a behaviorally based psychological treatment should be considered.

- Because of its prevalence and impact on daily functioning, the presence of significant physical or psychological symptoms in a female patient should alert any physician to the possible diagnosis of PMDD. For the treatment of severe psychological or physical symptoms causing functional impairment, sertraline and fluoxetine are clearly beneficial in carefully selected patients. Patients responding well to daily dosing may consider a trial of luteal-phase treatment. Limiting therapy to lower dosages (e.g., 20 mg of fluoxetine) and using intermittent dosing regimens may minimize adverse effects while preserving efficacy.

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