Evidence-Based Strategies for Achieving and Sustaining Full Remission in Depression: Focus on Metaanalyses

Raymond W Lam, MD, FRCPC[1], Sidney H Kennedy, MD, FRCPC[2]

The goal of therapy in the management of patients with major depressive disorder is to achieve and sustain remission. Extensive data on strategies to achieve remission have been published, and more recently, many of these data have been subject to systematic review and metaanalyses. This review compares data from metaanalyses and more recent trials on some of the therapies that may help to achieve remission. Strategies that have demonstrated improved rates of full remission in the treatment of depression include venlafaxine as initial antidepressant therapy, which has been shown to provide higher rates of remission when compared with serotonin reuptake inhibitors and tricyclic antidepressants. For patients who do not respond to initial medication treatment, treatments such as psychotherapy, exercise, light therapy, alternative medicines, and counselling have demonstrated benefits over placebo and may enhance remission rates when used in combination with antidepressants. Preventing relapse and sustaining the fully remitted state over the long term is also important in the management of depression. Continuing antidepressant therapy has been associated with excellent long-term outcomes for many patients. Randomized controlled clinical trials conducted in the last 5 years provide very good evidence to show that achieving and sustaining the fully remitted state is an attainable goal in the management of patients with depression.

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Information on author affiliations appears at the end of the article.

Clinical Implications

- Full symptom remission is a feasible goal for acute and long-term treatment of depression.
- Metaanalyses show that remission rates vary among antidepressant classes, such that serotonin norepinephrine reuptake inhibitors are superior to selective serotonin reuptake inhibitors in acute studies.
- Other somatic treatments and evidence-based psychotherapies can be used to optimize remission rates.

Limitations

- Nonadherence remains a significant factor in poor response to antidepressant treatment.
- There is still a limited evidence base for the choice and sequencing of interventions for depression.
- There are very few studies of long-term depression treatment outcomes.

***Key Words*:** *depressive disorders, antidepressants, evidence-based medicine, metaanalysis, psychotherapy, light therapy, complementary therapy*

The concept of full remission as the goal of treatment in major depressive disorder (MDD) is becoming increasingly recognized. Investigators have increasingly begun to use remission as an endpoint, and the current National Institutes of Mental Health–sponsored study, Sequenced Treatment Alternatives to Relieve Depression (STAR*D), views anything less than remission as treatment failure (1). Full remission is defined as the reduction of symptoms to within a normal range, while recovery also includes a return to premorbid levels of functioning (2,3). It is becoming increasingly recognized that recovery from MDD should be defined as asymptomatic status, not response, and the most recent Canadian guidelines target full remission as the goal of antidepressant therapy (4,5). In most clinical trials and in this paper, the term "response" indicates 50% reduction in depression scores, and the term "remission" refers to depression scores within the normal range (for example, the 17-item Hamilton Depression Rating Scale [$HDRS_{17}$] scores ≤ 7) (2).

Table 1 Definition of terms in metaanalytic studies

Metaanalysis	Statistical technique to summarize the results of several studies into a single estimate of their combined result; analyzes relative differences between treatment groups
Pooled analysis	Statistical technique to pool data from studies that have similar designs; analyzes absolute differences between treatment groups
Odds ratio (OR)	Odds of a treatment having an effect on outcome > 1: increases the odds of the outcome < 1: decreases the odds = 1: no effect
Relative risk (RR)	Risk of one outcome compared with another (similar to OR)
Effect sizes	Difference in outcome means divided by the within-study standard deviation: 0.2 = small, 0.5 = moderate, and 0.8 = large
95% confidence interval (95%CI)	Provides information about the likely range within which the actual value lies; if 95%CI encompasses 1 or infinity, result is not statistically significant for OR and RR
Intention-to-treat analysis	Analyzing the results according to the intended treatment to which a subject was randomized (as opposed to the treatment they actually received or completed)
Last observation carried forward	Method to account for missing data due to dropouts in a trial; assumes that outcome remains constant at the last observed value
Mixed-effects model repeated measures	Likelihood-based repeated measures statistical approach for handling missing data in a trial

A large number of data are available on strategies to achieve remission and prevent relapse (6). Many of these data have recently been assessed in metaanalyses. In this article, we will review these metaanalyses, as well as more recent randomized clinical trial data on therapies to achieve remission, including medication choice; optimizing, switching, and combining pharmacotherapy; concomitant psychotherapy; improving adherence; exercise; alternative therapy; light; and the role of patient preference and counselling. These data can help the clinician to individualize patient management by providing information on the strategies for which there is evidence of efficacy.

Methodologies

In 1979, Dr AL Cochrane wrote that, "It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or sub-specialty, adapted periodically, of all relevant randomized controlled trials" (7). Based on this premise, the Cochrane Collaboration was established to provide a library of up-to-date metaanalyses of randomized controlled trials (RCTs) using rigorous methodology and standardized reporting methods (8).

Metaanalysis and pooled analysis are considered to be the highest level of evidence for evidence-based medicine. A pooled analysis simply pools the individual data from several studies and analyzes the data as if they were from one big study. The limitation of a pooled analysis is that data can only be pooled from studies that have very similar study designs and outcomes. For example, depression studies using the $HDRS_{17}$ cannot be combined with those using the Montgomery–Asberg Depression Rating Scale (MADRS). Metaanalysis is a statistical technique to summarize the results of several studies into a single estimate of their combined result (9). It allows for analysis of data from studies that may have different parameters, for example, differences in duration or dosage.

The results from metaanalysis may be expressed as relative differences, odds ratios (ORs), or effect sizes (ESs) with 95% confidence intervals (95%CIs) (Table 1). The OR consists of the odds of an outcome (for example, remission) from one intervention divided by the odds of the outcome from a second. If an OR is greater than 1, then the first intervention is estimated to increase the odds of the outcome, and if less than 1, it decreases the odds (9,10). If the OR is exactly 1, there is no difference in outcome between the interventions. Relative risk (RR) is an estimate of the risk of experiencing a particular outcome. ORs and RRs are usually expressed between 95%CIs, which give the range within which there is a 95% chance the actual values lie (9,10). If the 95%CI encompasses 1 or infinity for OR or RR, the result is not statistically significant. The ES is the difference in outcome means divided by the within-study standard deviation (10). ESs of 0.2, 0.5, and 0.8 have been suggested to indicate small, moderate, and large effects, respectively (11).

Table 2 Recent metaanalyses of antidepressant strategies to achieve full remission

Study details	Treatment (*n*)	Remission rate, % HDRS ≤ 6 or ≤ 7 or RDS ≤ 5	ES on HDRS (95%CI)	OR for remission (95%CI)	Withdrawal for SE (95%CI)
Anderson and others (15) 102 RCT	SSRIs (5533) TCAs (5173)	—	SSRIs vs 0.03 (–0.03, 0.09) ns	—	12.4%***, vs TCAs[a] 17.3%
Smith and others (17) 32 RCT	VEN (2914) SSRIs (1857) TCAs (579) AMI (na; 1 trial) TRZ (na; 2 trials) MIR (na; 1 trial) Over all AD	—	VEN vs SSRI: 0.17 (0.08, 0.27)* TCA: 0.13 (0.19, 0.33)* AMI: –0.26 (–0.63, 0.10) ns TRZ: 0.23 (–0.02, 0.47) ns MIR: –0.23 (–0.55, 0.09) ns AD: 0.14 (0.07, 0.22)*	VEN vs SSRI: 1.43 (1.21, 1.71)* TCA:1.03 (0.46, 2.32) ns MIR: 0.69 (0.33, 1.43) ns AD: 1.36 (1.14, 1.61)*	VEN vs ADs: –0.004 (–0.029, 0.020) ns
Thase and others (18) 8 RCT	VEN (851) SSRIs (748) PBO (446)	45** 35** 25 VEN vs SSRI**[a]	—	VEN vs SSRI: 1.5 (1.3, 1.9)* PBO: 2.2* SSRI vs PBO: 1.4*	9%*** 7%*** 2% VEN vs SSRIs ns
Entsuah and others (19) 31 RCT	VEN (3078) SSRIs (3025) PBO (928)	41*** 34*** 24 VEN vs SSRI**[a]	—	VEN vs SSRIs: 1.30 (1.17, 1.44)* PRX: 1.19 (0.95, 1.48) ns FLX: 1.41 (1.22, 1.63)*	—
Schatzberg and Prather (20) 7 RCT	NEF (na) PBO (na)	32*** 21	—	—	—
Bech and others (21) 7 RCT	MIR (332) PBO (333) MIR (182) PBO (184) AMI (187)	— — — — —	MIR vs 0.49 (0.33, 0.64)* MIR vs 0.54 (0.33, 0.75)* –0.09 (–0.29, 0.12) ns AMI vs PBO 0.65 (0.44, 0.86)*		—
Casacalenda and others (29) 6 RCT	CBT, IPT, CT[b] (203) ADs (124) Control condtions (147)	46.3*** 46.4*** 24.4 PT vs AD: ns	—	—	—
Western and Morrison (28) 12 RCT	PT (na) Control conditions (na)	—	0.3*	—	—
Lawlor and Hopker (38) 14 studies	Exercise (na) PBO (na) CT (na)	—	Exercise vs 1.1 (0.6, 1.5)*[c] 0.3 (–0.1, 0.7) ns	—	—
Whiskey and others (44) 22 RCT	St John's wort (690) PBO (646) St John's wort (694) ADs (700)	—	—	St John's wort vs 1.98 (1.49, 2.62)* AD: 1.00 (0.90, 1.11) ns	St John's wort vs 1.04 (0.68, 1.58) ns 0.59 (0.52, 0.71)*
Thompson (52) 50 RCT	Light therapy (na) Control conditions (na)	—	—	Light therapy vs 3.11 (1.88, 5.15)*	—

[a]Asterisks indicates significant difference vs placebo or control condtions unless otherwise noted: * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$; ns = not significant ($P > 0.06$).

[b]Psychotherapy (PT) included cognitive-behavioural therapy (CBT), interpersonal therapy (IPT), and Beck's cognitive therapy (CT).

[c]ES values were calculated using the Beck Depression Inventory rather than the HDRS.

AD = antidepressants; AMI = amitriptyline; ES = effect size; FLX = fluoxetine; HDRS = Hamilton Depression Rating Scale; MIR = mirtazapine; na = not available; OR = odds ratio; PBO = placebo; PRX = paroxetine; RCT = randomized controlled trials; RDS = Raskin Depression Scale; SE = side effect; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants; TRZ = trazodone; VEN = venlafaxine

Clinical trial results are usually analyzed by intention-to-treat (ITT) or per-protocol (also known as observed-case) analyses. ITT refers to analyzing the results according to the intended treatment to which someone was allocated (as opposed to the treatment they actually received in the end) and accounts for any dropouts that may occur during a trial. The per-protocol analysis uses only data from those patients who received the treatment to which they were allocated. It may give a skewed outcome if there were many dropouts, for example, owing to side effects. In an ITT analysis, a last observation carried forward (LOCF) method is commonly used for data missing owing to dropouts. This method assumes that outcome remains constant at the last observed value. More recently, it has been suggested that a likelihood-based statistical approach called mixed-effects model repeated measures (MMRM) may better represent missing data (12,13).

Strategies to Achieve Full Remission: What is the Evidence?

Choice of Initial Antidepressant Therapy

Do different antidepressants offer different rates of remission (Table 2)? Previous metaanalyses generally support few or no overall differences in efficacy between selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) (10,14,15). TCAs may be more effective for the treatment of inpatients, and several analyses have suggested that amitriptyline is more effective than SSRIs (15,16). SSRIs are better tolerated than most TCAs, with significantly lower rates of treatment discontinuations owing to side effects (OR 0.73; 95%CI, 0.67 to 0.80) (15). However, these analyses mainly include studies that did not examine remission rates.

In 3 recent metaanalyses, the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine produced significantly higher rates of remission in the treatment of depression, compared with SSRIs (17–19). These analyses have consistently demonstrated higher remission rates with the use of venlafaxine as initial therapy, with ORs for remission ranging from 1.26 to 1.5, compared with SSRI, and OR 1.29, compared with TCAs. Remission rates were 41% to 45% with venlafaxine, 34% to 35% with SSRIs ($P < 0.001$), and 24% to 25% with placebo ($P < 0.001$) (18,19).

Pooled data from 7 RCTs, including 781 patients treated with nefazodone at dosages of 300 to 600 mg daily or placebo demonstrated significantly higher remission rates with nefazodone, compared with placebo (32% vs 21%; $P = 0.001$) (20).

A metaanalysis of 7 studies comparing the dual-acting agent mirtazapine with placebo or amitriptyline demonstrated significantly higher ESs with both mirtazapine and amitriptyline, compared with placebo (21). ESs were higher with amitriptyline, compared with mirtazapine, but not significantly so.

Optimizing, Switching, and Combining Pharmacotherapy

Clearly, a high proportion of patients will not achieve full remission with initial antidepressant therapy. Strategies to boost remission rates include first optimizing the dosage, then switching or combining antidepressants and other therapies (Table 3). Fava and colleagues compared 3 strategies of optimizing dosage or combining antidepressant therapy in patients with a partial or nonresponse to fluoxetine (20 mg daily) (22). Dosage optimization of fluoxetine (40 to 60 mg daily) was associated with nonsignificantly higher response rates, compared with fluoxetine plus lithium (300 to 600 mg daily) or fluoxetine plus desipramine (25 to 50 mg daily) (42.4%, 29.4%, and 23.5%, respectively). In contrast, continuing sertraline (100 mg daily) at the same dosage for an additional 5 weeks was more effective than doubling the dosage ($P < 0.05$) and was as effective as adding mianserin to therapy in 295 nonresponders to 6 weeks of open sertraline treatment (70%, 56%, and 67%, respectively) (23).

Switching within the same class of agents is generally a poor choice with the TCAs but may be an effective strategy with SSRIs (5). About 50% to 60% of patients will respond when switched to another SSRI (5,24). Combination antidepressant therapy was associated with significant benefits in a study in which bupropion was added to index antidepressant therapy in patients with inadequate response to venlafaxine, paroxetine, or fluoxetine. Over 30% of patients achieved remission; however, there was no control group in this study (25). Several recent open trials and RCTs support the benefits of atypical antipsychotics as effective augmentation strategies (26,27).

Psychotherapy

Psychotherapy has been shown to be as effective as antidepressant therapy and more effective than usual care in the management of patients with mildly to moderately severe depression (Table 2) (28,29). Western and Morrison assessed data from 12 RCTs of empirically supported psychotherapies and reported an ES of 0.3 with psychotherapy, compared with control groups (28). In an analysis of 6 RCTs, rates of remission in the psychotherapy group (primarily cognitive-behavioural therapy [CBT] and interpersonal therapy) were similar to those in the antidepressant group (TCAs and phenelzine) (46.3% and 46.4%) (29). Both rates were significantly better than rates in the control group (24.4%), but there

Table 3 Remission rates in recent clinical trials comparing optimization and augmentation

Study details	Treatment and dosage, mg (*n*)	Remission rate, % HDRS ≤ 7	Response rate, % ≤ 50% improvement HDRS
Fava and others (22)	FLX 40 (33)	42.4 ns[a]	—
4 weeks; *n* = 101; partial or no response to FLX 20 mg; $HDRS_{17}$ = 16.6	FLX 20 + DES (34)	29.4 ns	—
	FLX 20 + Li (34)	23.5 ns	—
Licht and Qvitzau (23)	SER 100	38	70
5 weeks; *n* = 295; no response to SER 100 mg; $HDRS_{17}$ = 23 mg	SER 200	29	56[b]
	SER 100 + MIA 30	44	67

[a]Not significantly different among treatments ($P > 0.05$). [b]Significantly different from SER 100 ($P < 0.05$).

DES = desipramine; FLX = fluoxetine; HDRS = Hamilton Depression Rating Scale; Li = lithium; SER = sertraline; MIA = mianserin

were no significant differences between active treatments. Discontinuation rates were significantly higher in the control group, compared with either active treatment group.

Several studies have demonstrated that the combination of antidepressants and psychotherapy is more effective than antidepressant therapy alone (Table 4) (30,31). In one study, remission rates with the combination of psychotherapy and antidepressants were more than double those seen with antidepressant therapy alone at both 8-week (19.3% vs 8.3%) and 24-week (37.3% vs 15.4%) assessments (31). However, the low remission rates with antidepressant therapy are difficult to explain. Most of the patients did not suffer from chronic depression; antidepressant therapy was optimized or combined; and although the dropout rates with antidepressants were high at 24 weeks (40% in the antidepressant group and 22% in the combined group), they were quite low at 8 weeks (5% and 6%, respectively). Combination therapy has also been shown to be cost-effective compared with antidepressants alone (30).

Improving Adherence

Treatment guidelines recommend that antidepressant treatment be continued for at least 6 to 9 months after remission to ensure maximal improvement and to prevent relapse (5), but naturalistic studies show that this occurs in less than one-half of patients in primary care (32). In addition, dropout rates are high, with 1 in 3 patients not completing their treatment (33,34). A recent review of 32 studies of adherence (through 1999) found that available data were too heterogeneous to allow comment on which interventions were most effective, but they did consistently show improved adherence with patient education and other interventions (34). In a 29-week RCT, a program specifically designed to enhance adherence to sertraline had no effect on remission rates, treatment adherence, or HDRS scores among patients receiving sertraline (35). However, the program did increase patient satisfaction with treatment.

Interventions addressing adherence may be more important in the prevention of relapse than in the acute response to therapy (36,37). Patients randomized to a multifaceted education program including systematic patient education, 2 psychoeducational visits with a specialist, shared decision making regarding maintenance pharmacotherapy, and telephone and mail monitoring of medication adherence and depressive symptoms experienced a mean of 13.9 additional depression-free days during a 12-month period (36). Similarly, a RCT found that receiving educational materials by mail did not affect acute rates of treatment compliance or outcome in depression patients, but relapse rates were lower (37).

Exercise

A metaanalysis of studies assessing the role of exercise in the management of depression included 14 studies, most of which had important methodological weaknesses (Table 2) (38). Many studies included community cohorts rather than strictly diagnosed patients with MDD. Exercise reduced symptoms of depression significantly more than no treatment (ES 1.1; 95%CI, 0.6 to 1.5), and benefits were similar to those of cognitive therapy (ES 0.3; 95%CI, –0.1 to 0.7). More recent RCTs suggest that exercise may be associated with less depressed mood and significant improvements in HDRS scores (39–42). In a RCT comparing exercise classes or health education talks for 10 weeks, a significantly higher proportion of patients in the exercise group (55% vs 33%) experienced a greater than 30% decrease in HDRS scores (40).

Complementary Treatment

A recent review of the evidence for the effectiveness of complementary and self-help treatments for depression included 37 treatments grouped under the categories of medicines, physical treatments, lifestyle changes, and dietary changes (43). The treatments with the best evidence of effectiveness were St John's wort and exercise. A metaanalysis of 22 RCTs including St John's wort found that the OR for response was almost twice that of placebo and not significantly different from antidepressant therapy (Table 2) (44). In the largest

Table 4 Remission rates in clinical trials of novel therapies

Study details	Treatment (*n*)	Remission rate, % HDRS ≤ 6 or ≤ 7	
Lecrubier and others (46)	St John's wort (186)	24.7*	
6 weeks; *n* = 375;	PBO (189)	15.9	
$HDRS_{17}$ = 21.9			
HDTS group (47)	St John's wort (113)	27.0% vs PBO, ns	
8 weeks; *n* = 340;	SER (109)	27.0% vs PBO, ns	
$HDRS_{17}$ = 22.8	PBO (116)	37.0%	
		HDRS 8 and CGI-I 1 or 2	
de Jonghe and others (31)		8 weeks	24 weeks
24 weeks; *n* = 167;	PT, SPSP, + ADs (83)	19.3%*	37.3***, vs ADs alone
$HDRS_{17}$ = 20.43	ADs alone (84)	8.3%	15.5
Bedi and others (55)	Randomized to	RDC < 4 at 8 weeks	12 months
Chilvers and others (56)	Counselling (52)	48	17
8 weeks + 12 months; *n* = 323	ADs (51)	57	41**, vs counselling
	Patient preference		
	Counselling (140)	49	34
	ADs (80)	40	21*, vs counselling

Asterisks indicate significant differences: *$P \leq 0.06$; **$P \leq 0.01$; ***$P \leq 0.001$; ns = not significant ($P > 0.06$).

ADs = antidepressants; CGI-I = Clinical Global Impression Scale-Improvement; HDTS = *Hypericum* Depression Trial Study Group; PBO = placebo; PT = psychotherapy; RDC = Research Diagnostic Criteria; SER = sertraline; SPSP = Short Psychodynamic Supportive Psychotherapy

study (n = 200), no significant differences were found in response rates, but St John's wort had higher remission rates, compared with placebo (14.3% vs 4.9%; $P = 0.02$) (45). Two additional recent trials have reported conflicting results; one found higher remission rates with St John's wort, compared with placebo (24.7% vs. 15.9%; $P = 0.03$) (46), while the other found no significant differences in treatment with St John's wort, sertraline, or placebo (Table 4) (47).

Two RCTs have reported significant benefits of the use of the omega-3 fatty acid ethyl-eicosapentaenoic acid (E-EPA), compared with placebo, as an adjunct to antidepressant treatment (48,49). Response rates (50% reduction in HDRS) were higher among patients receiving E-EPA augmentation, compared with those receiving placebo (53% vs 29%; $P = 0.02$) (49). Remission rates were not reported in either study.

Light

Light therapy has demonstrated efficacy in the treatment of seasonal affective disorder (SAD), or winter depression (50–52). In an earlier report, Terman and colleagues analyzed data from 332 individual patients from 14 research centres, using a pooled clustering technique (50). Overall, 2500-lux intensity light exposure for at least 2 hours daily for 1 week resulted in significantly more remissions when administered in the early morning (53%) than in the evening (38%) or at midday (32%). All 3 times were significantly more effective than dim light administered as a control condition (11%). A subsequent metaanalysis conducted in 1999, including 39 studies, confirmed the greater benefit of more intense light, with strong light (ES 2.94) being significantly more effective than medium light (ES 1.74, $P < 0.05$) or dim light (ES 1.13, $P < 0.05$) (Table 2) (51).

A recently reported metaanalysis of RCTs included 50 studies (52). Analysis of 14 studies that included control conditions in patients with SAD found that light exposure produced significantly more responders (OR 2.83) and remitters (OR 3.11), compared with control conditions. Morning light was associated with a higher rate of remission (OR 1.93) than evening light. There was no overall benefit of light therapy in studies of patients with nonseasonal affective disorders (non-SAD), but there were very few controlled studies available. In contrast, another systematic review found that bright light was more effective than control conditions not only in SAD (ES 0.84; 95%CI, 0.60 to 1.08) but also in non-SAD (ES 0.55; 95%CI, 0.23 to 0.87) (53).

Counselling and Patient Preference

Selection bias has always been a concern for clinical trials because patients must volunteer to be randomized to treatment. One assumption has been that patients may have better outcomes with a treatment that they prefer. Volunteer bias may be particularly important when psychotherapy and

pharmacotherapy are being compared, because surveys show that most patients diagnosed with depression prefer counselling to medications (54). To address this issue, recent studies offer patients the opportunity to participate in a study with random treatment assignment, but if they decline, they are able to choose the treatment that they prefer. In these randomized patient-preference studies, the outcomes of patients in the randomized trial can thus be compared with those who preferred a particular treatment.

In 2 studies designed to evaluate the efficacy of counselling or psychotherapy for patients in primary care, there was an inconsistent relation between being allowed to choose treatment and short- and long-term outcome. The first study allowed a mixed recruitment strategy in which patients were either randomized to antidepressants or counselling ($n = 103$) or given their choice of treatment ($n = 220$) (Table 4) (55,56). The 2 treatments were equally effective at 8 weeks, and expressing a preference for either treatment conferred no additional benefit on outcome. At 12 months, there was no overall difference between randomized groups in Beck Depression Inventory (BDI) scores, but patients randomized to antidepressants had significantly higher remission rates than those randomized to counselling (41% vs 17%; $P = 0.01$). Meanwhile, patients in the preference arm who chose counselling had better outcomes than those randomized to counselling and a trend to better remission rates, compared with those who chose antidepressants (34% vs 21%; $P = 0.06$) (56). The low remission rate in patients choosing antidepressants may be owing, in part, to the very low completion rates in the preference arm (25%), compared with patients randomized to antidepressants (53%). These results suggest that patient preference may improve outcomes with counselling but may not make a difference with pharmacotherapy.

The second randomized patient-preference trial compared nondirective counselling, CBT, and usual general practitioner (GP) care (57,58). In addition to the randomized arms ($n = 197$), the trial also had patient-preference arms where patients had the option of a specific choice of treatment ($n = 137$) or the option to be randomized between the psychological therapies only ($n = 130$). At 4 months, patients randomized to nondirective counselling or CBT showed significantly more improvement in BDI scores and were more satisfied with their care than those randomized to usual GP care. There was no significant difference between the 2 psychological therapies. At 12 months, there were no longer significant differences in outcome among the 3 treatment groups, but patients who received nondirective counselling were more satisfied than those in the other 2 groups (58). Patients expressing a preference for treatment did not differ in outcomes at 4 or 12 months, compared with the randomized patients. These results suggest that, when a choice of psychological treatments is offered, patient preference does not affect outcome, compared with randomization.

Strategies to Sustain Remission

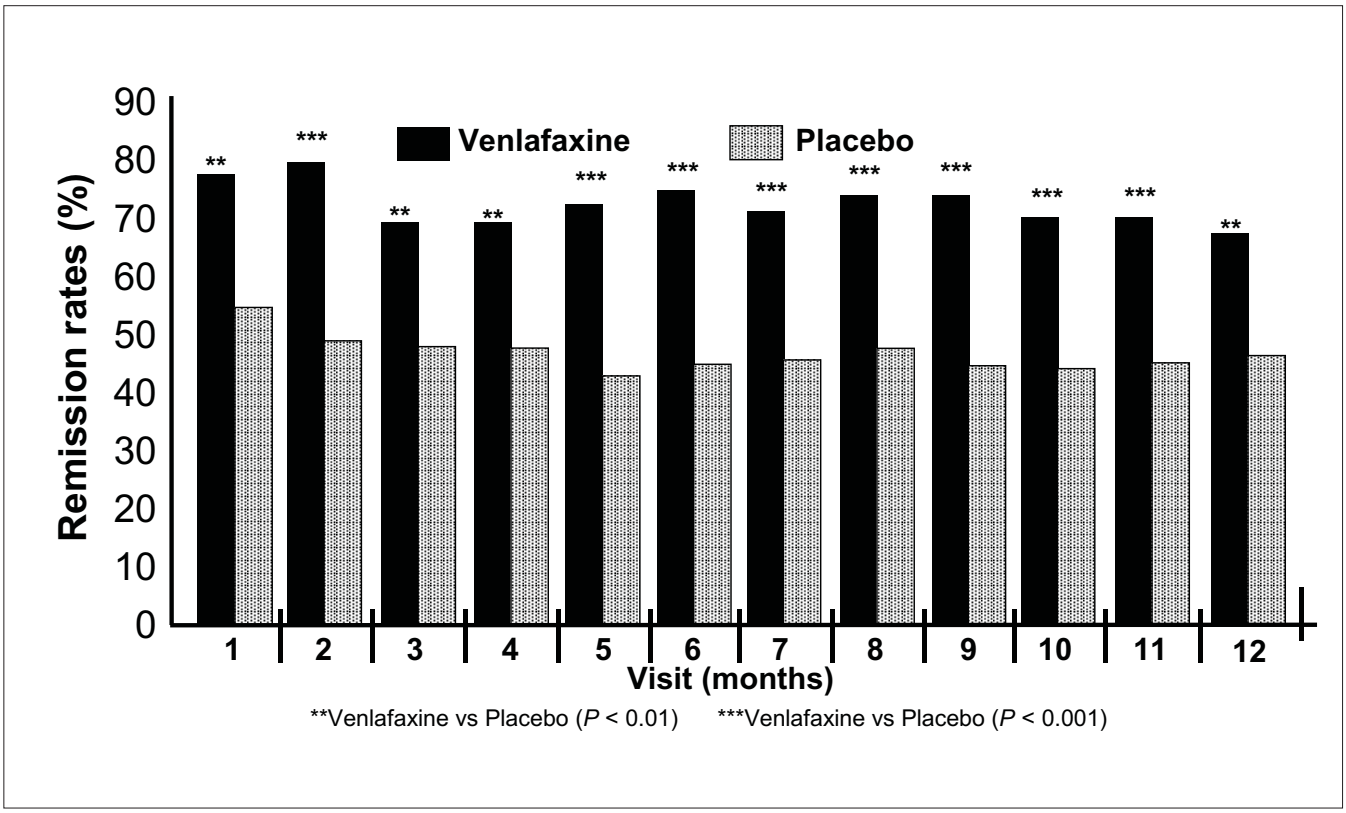
Achieving full remission with acute therapy is one of the most important strategies in the prevention of relapse and recurrence. Anything less than remission leaves patients with residual symptoms and an increased risk of relapse and recurrence (6,59). In both RCTs and open-label continuation studies, continuing therapy with antidepressants or psychotherapy for 6 to 12 months has been demonstrated to be protective against relapse and recurrence (6,47,60–66). A metaanalysis of 31 randomized relapse-prevention trials involving 4410 patients found that continuing treatment with antidepressants reduced the odds of relapse by 70% (95%CI, 62 to 78; $P < 0.0001$), compared with placebo (67). The average rate of relapse was only 18% with continued antidepressant therapy, compared with 41% with placebo.

Preventing relapse or recurrence is a critical outcome, but equally important is the maintenance of the fully remitted state over an extended period. In a study of patients with chronic depression and at least a partial response to 12 weeks of sertraline or imipramine therapy, 67% (92/137) of sertraline-treated and 70% (62/88) of imipramine-treated patients entering the continuation phase in full remission sustained the remission during 16 weeks of continuation therapy (63). Of the patients who entered the continuation phase in response, 43% of sertraline-treated patients and 41% of imipramine-treated patients went on to achieve full remission.

In a 40-week, double-blind continuation study, patients in remission after 8 to 12 weeks of mirtazapine therapy were randomized to mirtazapine or placebo for up to 6 months (62). Remission was sustained throughout the trial in 72% (55/76) of patients who received mirtazapine at the end of the continuation phase, compared with only 47.5% (38/80) of placebo-treated patients.

Venlafaxine has been studied in 2 long-term, double-blind maintenance trials (one of 6 months' duration and one of 1 year's duration) after a sustained response (60,61). Reanalysis of these 2 studies including only those patients in full remission ($HDRS_{17} \leq 7$) at the time of randomization found higher rates of remission in the venlafaxine groups, compared with the placebo groups, at both 6 months (65% and 37%) and 12 months (67% and 46%; Figure 1) (68,69). In addition, analysis of the remission rates on a monthly basis during the 6-month open-label phase in the recurrence study showed

Figure 1 Remission rates over time among patients who achieved remission during the open-label phase prior to randomization (intent-to-treat population). Data are from Nemeroff and others (69).



that, although most patients achieved remission during the first 2 months of therapy, an additional 10% of patients went on to achieve remission during the next 4 months (69).

Preventing relapse or recurrence is a critical outcome, but equally important is the maintenance of the fully remitted state over an extended period. With continuing antidepressant and (or) psychological therapy, over 70% of patients can sustain remission over the long term.

Summary

The concept of remission as the goal of treatment in MDD is becoming increasingly recognized. Metaanalyses have shown that several strategies have demonstrated improved rates of remission in the treatment of MDD. The choice of initial therapy can be a factor, with the SNRI venlafaxine demonstrating higher rates of remission, compared with SSRIs. However, a high proportion of patients will not achieve full remission with initial antidepressant therapy. Psychotherapy, exercise, light therapy, alternative medicines, and counselling have demonstrated efficacy over placebo or usual care but do not appear to have any significant advantage over antidepressant therapy. Although there is still a very limited evidence base, the use of these strategies in combination with antidepressants may accelerate or enhance remission rates. Patient preference appears to have little influence on remission rates with antidepressants, but counselling or CBT may be more effective in patients expressing a preference for psychological treatment.

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[1]Professor, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia
[2]Professor, Department of Psychiatry, University of Toronto; Psychiatrist-in-Chief, University Health Network, Toronto, Ontario.
Address for correspondence: Dr RW Lam, Professor and Head, Division of Clinical Neuroscience, Department of Psychiatry, University of British Columbia, 2255 Wesbrook Mall, Vancouver, BC V6T 2A1
e-mail: r.lam@ubc.ca