Pharmacotherapy to sustain the fully remitted state

Sidney Kennedy, MD; Roger McIntyre, MD; Angelo Fallu, MD; Raymond Lam, MD

Kennedy, McIntyre — Mood and Anxiety Disorders Program, Department of Psychiatry, University of Toronto, Toronto, Ont.; Fallu — Woodward Clinic, Sherbrooke, Que; Lam — Department of Psychiatry, University of British Columbia, Vancouver, BC.

Full remission should be the goal of antidepressant therapy; anything less leaves the patient with residual symptoms and an increased risk of relapse and recurrence. Most antidepressant agents offer similar rates of response, but there are some differences in the ability of different agents to promote a full remission. The greatest chance of achieving full remission occurs early in the course of treatment; thus, initial antidepressant strategies should be those that have the greatest therapeutic potential. Other strategies that may help improve the chances of achieving full remission include optimizing drug dosages and using combination and augmentation strategies. Failure to achieve full remission and early discontinuation of antidepressant therapy have been associated with a greater incidence of relapse and recurrence. Continued antidepressant therapy has clearly been shown to effectively reduce the probability of relapse and recurrence by about half compared with placebo. Therefore, once a patient achieves remission, it is important to continue the same antidepressant therapy for at least 6–12 months and, for many patients, considerably longer. Medication should continue at the dose that was initially effective because using low-dose maintenance therapy appears to decrease the protective benefits.

Toute thérapie aux antidépresseurs devrait viser à produire une rémission complète. Toute rémission incomplète laisse au patient des symptômes résiduels et un risque accru de rechute et de récidive. La plupart des antidépresseurs produisent des taux semblables de réponse, mais la capacité de différents agents de produire une rémission complète diffère un peu. C'est au début du traitement que la chance de rémission complète est la meilleure. Les traitements initiaux aux antidépresseurs devraient donc être ceux qui offrent le plus de potentiel thérapeutique. D'autres stratégies qui peuvent aider à améliorer les chances de rémission complète comprennent l'optimisation des posologies et le recours aux stratégies de combinaison et d'augmentation. On a établi un lien entre l'incapacité de produire une rémission complète et l'interruption précoce de la thérapie aux antidépresseurs, d'une part, et une incidence plus importante de rechutes et de récidives, de l'autre. Il a été démontré clairement que la thérapie continue aux antidépresseurs réduit d'environ la moitié la probabilité de rechute et de récidive comparativement au placebo. Par conséquent, lorsqu'un patient parvient au stade de la rémission, il importe de poursuivre la même thérapie aux antidépresseurs pendant au moins six à 12 mois, et beaucoup plus longtemps dans le cas de certains patients. Il faudrait poursuivre la médication à la posologie qui s'est révélée efficace au début parce qu'une thérapie d'entretien à faible dose semble réduire les avantages de la protection.

Correspondence to: Dr. Sidney Kennedy, University Health Network, 200 Elizabeth St., 8th Flr, Eaton Wing, Rm. 222, Toronto ON M5G 2C4; fax 416 340-4198; sidney.kennedy@uhn.on.ca

Introduction

An important paradigm shift among practising psychiatrists is the acceptance of unipolar depression, not as a single episode illness, but rather as a recurrent and often chronic debilitating condition.[1] Between 15% and 20% of depressed patients experience a chronic course of illness, and up to 80% experience a recurrent course of illness.[2-4] Antidepressant treatment for recurrent depression is intended to reduce the probability of, as well as the duration of, future episodes and to confer both the pharmacological and economic benefits of improved quality of life and reduced medical costs.[5]

The primary goal of patient and therapist in the treatment of depression is to achieve full remission. This is the optimal state for the patient's well being, and residual symptoms are known to predispose to further episodes of depression. A key question in the treatment of major depressive disorder (MDD) is how long to continue pharmacotherapy. Although antidepressant therapy may suppress symptoms, it may not immediately correct the underlying disorder.[6,7] As a result, there may be a gap of several weeks or months between symptom control and episode resolution.[8] Early discontinuation of therapy is likely to result in relapse for about 50% of patients.[9,10]

Response, remission, relapse and recurrence

Our definitions of response, remission, relapse and recurrence are consistent with those described by Frank and colleagues.[11] The goal of therapy is full remission; anything less leaves patients with residual symptoms and an increased risk of recurrence. Full remission is the virtual elimination of symptoms and a return to premorbid levels of functioning.[11] "Relapse" refers to the return of sufficient symptoms to cause an individual to again meet diagnostic criteria for the illness after a discrete period of wellness. In clinical trials, between 50% and 70% of patients respond to antidepressant therapy but only 25%–35% of patients experience full remission.[12,13] This is very disturbing; less than half of treated patients achieve full remission, and even after a reasonable duration of treatment, most will experience some residual symptoms. A return to a premorbid level of functioning has probably been the most underemphasized portion of the treatment plan for depressed patients.

Since the distinction between continuation therapy (to prevent relapse) and maintenance therapy (to prevent recurrence) is somewhat arbitrary, these data will focus on the acute phase and long-term maintenance phase outcomes. Acute therapy is required to achieve full remission, and maintenance therapy is needed to sustain the fully remitted state.[14]

Time to response and remission

In general, evidence of improvement (variously defined as a decrease of 20% or 30% in Hamilton Rating Scale for Depression [HAM-D] baseline score) within 2 or 4 weeks of initiating treatment predicts a favourable outcome after 8 weeks of antidepressant treatment. The corollary is that significantly fewer patients who have not shown this modest level of early response go on to achieve response or remission at 8 weeks, compared with those in the "improvement and early response" group.[15,16] In the first of 2 studies involving independent patient populations, Nierenberg et al[15] reported that only 19% of those who did not show at least a 20% drop in HAM-D score at 4 weeks, and 6% of those who had not shown a similar drop at 6 weeks went on to achieve a response (50% reduction in HAM-D) after 8 weeks of treatment with fluoxetine (20 mg daily).[15] In the second study involving a larger population of depressed subjects, the same research group reported that over 75% of eventual responders to 8 weeks of fluoxetine therapy had shown at least a 30% decrease in symptoms by week 4.[16] Conversely, those who had not experienced improvement by weeks 4 or 6 had a 73%–88% chance of nonresponse by the end of the 8-week trial. Evidence of an early trajectory of response has also been reported for paroxetine and for venlafaxine.[17,18]

The same findings appear to be true for remission. Patients have the greatest chance of achieving full remission early in their treatment course. During the first 6 months of treatment, 50% of patients achieved full remission in a study conducted in the United Kingdom. Over time, the cumulative likelihood of full remission was reduced, and by months 13–15 only 5% of patients were in remission.[19] In an Irish study, the probability of remission in 100 consecutive depressed inpatients was determined over 18 months.[20] The cumulative probabilities of remission onset by 3 and 18 months were 67% and 82%, respectively, and there was a 25% probability of relapse, of which more than half occurred in the first 2 months after remission.

This implies a window of opportunity during which the patient has a greater likelihood of achieving remission. Remission occurs early in the treatment process, suggesting the need for aggressive first-line strategies that are capable of producing full remission. Given that functional improvement lags behind symptom improvement, the faster remission can be achieved, the sooner the patient will experience a restored quality of life.

Achieving full remission

Optimization, augmentation and combination therapy

A number of strategies should be considered for patients who fail to achieve full remission with an initial therapeutic trial. During initial therapy, the patient should be monitored and the pharmacotherapy optimized.[21] This includes assessing adherence and comorbidity and adjusting the dose. In a US survey of 801 practising clinicians designed to assess strategies used in cases where selective serotonin reuptake inhibitors (SSRIs) are ineffective, 84% of respondents chose to increase the dose.[22] This can be particularly useful with agents that have a linear dose–response curve. Yet, in a UK survey of a large prescription database for antidepressant use, less than 5% of family practitioners had actually increased the initial dose.[23] Switching agents was the choice of only 7% of respondents; however, this may be preferred when the side-effect burden is too high with high-dose monotherapy. Although data are limited on the efficacy and safety of combination strategies, augmentation or combination was the choice of 10% of clinicians. When asked about their preferred agent, 30% chose bupropion and 22% lithium. Largely on the basis of anecdotal evidence, the use of augmentation or combination strategies is recommended for partial responders, whereas in the absence of any response, switching medications may be preferred.[21]

Strategies that involve combining pharmacotherapy and psychotherapy, such as cognitive behaviour therapy or interpersonal psychotherapy may also enhance remission rates. Some patients, particularly those who have been depressed for a long time, may need additional help to stop the negative thought patterns they have developed. In a small pilot study, patients who received cognitive behaviour therapy for residual symptoms after successful drug therapy showed significantly increased remission rates.[24]

Antidepressant choice

Aggressive initial treatment should be implemented with drugs that offer the greatest therapeutic potential and the best chance to induce full remission.[25] In general, antidepressants from the various classes have not shown significantly different response rates. A meta-analysis of 102 trials involving 10 706 patients demonstrated no significant differences in overall efficacy, as measured by effect sizes, between SSRIs and tricyclic antidepressants (TCAs).[26] In addition, no significant differences in efficacy were noted between any of the individual SSRIs and individual TCA comparators. However, TCAs may be more effective in inpatients, and amitriptyline was more effective than SSRI comparators. A systematic review of 186 randomized controlled trials also showed superior overall efficacy of amitriptyline compared with other TCAs and SSRIs even when dropouts were included as treatment failures.[27]

Table 1 reviews some of the recent clinical trials that have focused on achieving full remission, rather than just response. Separate trials were identified comparing reboxetine (not yet available in Canada), nefazodone, moclobemide, mirtazapine and venlafaxine to TCAs or SSRIs. Therapy with bupropion has demonstrated response rates comparable to various SSRIs (e.g., sertraline and paroxetine),[28,29] but no studies reporting rates of full remission were identified. Comparisons among studies should be made with caution because study parameters including patient types, dosing and severity of illness varied significantly. No agent significantly and consistently was associated with higher remission rates than their TCA or SSRI comparator, with the exception of venlafaxine.

Treatment with SSRIs generally results in remission rates of about 20%–39%, whereas remission rates with TCAs were 46%–53%. Remission rates with reboxetine, a selective norepinephrine reuptake inhibitor, were about 42%.[30] Nefazodone acts primarily as a serotonergic 5-HT$_2$ receptor antagonist as well as a weaker serotonin reuptake inhibitor.[31] It exhibited rates of full remission of 62% in one study but only 22% in another study with a more stringent definition of remission.[32,33]

Moclobemide is a reversible inhibitor of monoamine oxidase A. Remission rates of 30%–47% have been reported with moclobemide treatment, which is comparable to those seen with SSRIs and the tricyclic clomipramine.[34–36] However, in one of these studies, moclobemide was associated with a higher rate of

nonresponse or worsening of depression than clomipramine.[35] Mirtazapine acts to increase serotonin and norepinephrine by blocking presynaptic receptors. The studies involving mirtazapine did not report significantly higher remission rates for mirtazapine than for the SSRI fluoxetine[37] or the tricyclic amitriptyline.[38]

Remission rates for venlafaxine, a dual-acting serotonin and norepinephrine reuptake inhibitor, range from 37% to 67%. These rates are significantly higher than those of comparator SSRIs and the tricyclic imipramine.[39–43] The higher rates of full remission with venlafaxine were replicated in a recent meta-analysis of 8 randomized trials comparing venlafaxine and SSRIs in over 2000 patients.[44] Patients had a 50% greater likelihood of achieving remission when treated with venlafaxine than they did when treated with an SSRI.

Table 1: Rates of full remission in recent clinical trials of antidepressant therapy for depression

Study	Treatment duration and dosage, mg/d	Response,* % of patients	Remission, % of patients	Remission criteria
Katona et al[30] n = 347	8 wk RBX, 4–6 IMP, 50–100	55 57	42 50	HAM-D$_{21}$ ≤ 10
Cohn et al[32] n = 77	8 wk NFZ, 200–600 IMP, 100–300	64 61	62 53	HAM-D$_{17}$ ≤ 10
Keller et al[33] n = 681	12 wk NFZ, 300–600 CBASP and combination	55 52 85†	22 24 42	HAM-D$_{24}$ ≤ 7
Danish University Antidepressant Group[35] n = 115	6 wk MCL, 400 CMI, 150	49 71‡	19 33	HAM-D$_{17}$ ≤ 7
Lapierre et al[34] n = 128	6 wk MCL, 200–600 FLX, 20§–40	54 55	47 38	HAM-D$_{17}$ < 10
Sogaard et al[36] n = 197	12 wk MCL, 300 SRT, 50	63 65	30 39	HAM-D ≤ 7
Stahl et al[38] n = 387	6 wk MRT, 5–35 AMT, 40–280	48 51	31 28	HAM-D$_{17}$ ≤ 7
Wheatley et al[37] n = 123	6 wk MRT, 15–60 FLX, 20–40	66 47	23 25	HAM-D$_{17}$ ≤ 7
Mehtonen et al[39] n = 85	8 wk VFX, 150 SRT, 100	81 67	67‡ 36	HAM-D$_{21}$ < 10
Poirier and Boyer[40] n = 122	4 wk VFX, 200–300 PRX, 30–40	52‡ 33	42‡ 20	HAM-D$_{17}$ ≤ 10
Ballus et al[41] n = 84	12 wk VFX, 75–150 PRX, 20–40	75‡ 64	59‡ 31	HAM-D$_{21}$ ≤ 8
Rudolph and Feiger[42] n = 198	8 wk VFX, 75–225 FLX, 20–60	57 50	37‡ 22	HAM-D$_{21}$ ≤ 7
Lecrubier et al[43] n = 153	13 wk VFX, 75–150 IMP, 75–150	83 66	63‡ 46	CGI = 1¶

Note: AMT = amitriptyline; CMI = clomipramine; CBASP = cognitive behavioural analysis system of psychotherapy; FLX = fluoxetine; HAM-D = Hamilton Rating Scale for Depression; IMP = imipramine; MRT = mirtazapine; MCL = moclobemide; NFZ = nefazodone; PRX = paroxetine; RBX = reboxetine; SRT = sertraline; VFX = venlafaxine.
*"Response" was defined as a HAM-D or MADRS score reduction of 50% from baseline.
†$p < 0.001$ v. monotherapies.
‡$p ≤ 0.05$.
§FLX could be administered 20 mg every other day.
¶"Very much improved."

It has been hypothesized that the efficacy of antidepressants that act at more than one pharmacologic site (e.g., serotonin and norepinephrine reuptake inhibition) may be superior to that of SSRIs.[45] However, in a meta-analysis of 105 trials, Freemantle et al[46] did not find any relation between postulated mechanisms of action of antidepressants (i.e., serotonin or norepinephrine reuptake inhibition, 5-HT$_2$ receptor antagonism or combined actions) and relative efficacy.[46] This suggests that the question of how drug actions relate to efficacy may await a better understanding of downstream intracellular effects and also suggests that higher rates of remission with the dual-acting serotonin and norepinephrine reuptake inhibitor, venlafaxine, cannot be generalized to other agents simply on the basis of multiple mechanisms of action.

Given the risks associated with partial response, future studies comparing antidepressant strategies should turn their attention to full remission as an endpoint rather than simply response.

Factors affecting rates of relapse and recurrence

Residual symptoms

Epidemiological and clinical data support the goal of treating depressed patients to wellness or full remission.[25] The persistence of residual symptoms after treatment is a sign of a poor prognosis and a primary risk factor for relapse.[47–49] The impact of level of recovery on the probability of relapse was demonstrated in over 230 patients followed naturalistically for more than 10 years.[47] Judd and colleagues reported that patients who had residual symptoms after recovery relapsed 3–5 times faster than those who had recovered fully. In addition, residual symptoms were reported in 19 (32%) of 60 patients who had remitted to below the threshold for major depression.[48] This study also found residual symptoms to be strong predictors of early relapse, which occurred in 76% of patients with residual symptoms and 25% of those without.

Early discontinuation of antidepressant therapy

It has been suggested that antidepressants suppress depressive symptoms before acting on the pathophysiology underlying the disorder, during which time patients are vulnerable to a relapse if medication is withdrawn.[8,50] Continuing antidepressant therapy for 4–9 months after the remission of acute symptoms has been demonstrated to reduce the likelihood of relapse or recurrence of depression.[51,52]

A study to assess adherence to guidelines and relapse, using a Medicaid database from 1989 to 1994, followed the progress of 4052 adult patients for between 6 months and 2 years.[51] The guidelines were those published by the Agency for Health Care Policy and Research, which suggest acute treatment for 6–8 weeks, followed by 4–9 months of continuation treatment once depressive symptoms have resolved.[52] These guidelines also call for switching or adding of antidepressants for patients who do not respond adequately during the acute phase. Less than 30% of the patients in this study received antidepressant treatment that was even minimally consistent with the guidelines, and 24% of patients experienced a relapse or recurrence during their follow-up period. Those patients who continued therapy with their initial antidepressant were the least likely to experience relapse or recurrence, while those who discontinued their antidepressant early were the most likely. Even after adjusting for severity of illness and comorbidities, the continuous use of a single antidepressant from the start of a depressive episode was related to the greatest reduction in probability of relapse or recurrence.[51] The indicator of relapse or recurrence in this study was based on paid Medicaid claims, and this may mean that some patients who had a relapse or recurrence would not be counted as such.

Similar results were reported in an analysis of almost 7500 patients in a UK primary care database.[23] The patients who continued their initial antidepressant had a significantly lower rate of relapse than those who discontinued antidepressant therapy within 120 days (20% v. 23%, $p = 0.04$). In this analysis, relapse or recurrence was defined as any reinitiation of antidepressant treatment or an event (i.e., suicide, referral to psychiatrist, admission to hospital or emergency room for mental disorder or electroconvulsive therapy [ECT]) during the 18-months after a 6-month treatment period. Relapse during the first 6 months, a time when the occurrence of relapse is generally high, was not included. It has also been demonstrated that many patients with mood disorders who received treatment for past episodes do not seek or receive care for subsequent ones.[53] This may further contribute to significantly underestimated relapse rates in these studies.

In an attempt to prospectively determine the optimal length of therapy for patients with major depression, a long-term, placebo-controlled continuation study was carried out. Almost 400 patients who were treated to remission with fluoxetine were then randomly assigned to receive double-blind treatment in 1 of 4 groups: 50 weeks of placebo, 14 weeks of fluoxetine and then 36 weeks of placebo, 38 weeks of fluoxetine and then 12 weeks of placebo, or 50 weeks of fluoxetine.[54] Relapse rates were significantly lower with fluoxetine compared with placebo after 24 total weeks of treatment (fluoxetine 26.4%, placebo 48.6%, $p < 0.001$) and after 38 total weeks of treatment (fluoxetine 9.0%, placebo 23.2%, $p < 0.04$). After 62 total weeks of treatment, relapse rates were not significantly different between the groups (fluoxetine 10.7%, placebo 16.2%). However, the study group in the last interval was small because of patient attrition over the year of treatment, and there was not enough statistical power to detect small treatment effects. In agreement with current guidelines, these results demonstrate that patients who are treated acutely with fluoxetine to achieve remission should continue treatment for at least an additional 26 weeks to minimize the risk of relapse.[12]

Maintenance dose

It is generally accepted that decreasing the effective dose during acute TCA therapy results in increased rates of relapse.[11] This also appears to be the case with at least one SSRI. In a small, open-label study of the feasibility of reducing the dose of citalopram for long-term maintenance therapy,[55] when responders to citalopram, 40 mg/day, continued with maintenance therapy at a dose of 20 mg/day, recurrence occurred in 50% of patients during the 2-year maintenance period. This study lacked a control group, but suggested that a dose reduction of citalopram during the maintenance phase was linked to a decrease in prophylaxis. Therefore, a full dose of antidepressant is strongly recommended in prophylactic therapy of patients with recurrent major depression. As the clinical cliché states: "The dose that gets you well, keeps you well."

Antidepressant tolerance

Clinical folklore suggests that tolerance to antidepressants or "breakthrough depression" occurs with all antidepressants. This relapse or recurrence of depression while on antidepressant maintenance therapy has been experienced by patients treated with monoamine oxidase inhibitors, tricyclics and SSRIs; it is reported to occur in 9%–57% of patients.[56] Proposed causes of this real or apparent tolerance include pharmacological tolerance, pharmacokinetic changes, unrecognized rapid cycling, prophylactic inefficacy and changes in disease due to drug therapy or independent of drug therapy. Noncompliance is often suggested as a probable cause of loss of efficacy, but reduced therapeutic contact and a loss of nonspecific "placebo effects" may also contribute to this "tachyphalaxis."

Other factors that have been found to affect relapse and recurrence rates include comorbidities and severity of illness.[51] Early onset of depression (< 20 years of age) and greater chronicity have also been associated with a poorer prognosis.[57]

Prevention of relapse and recurrence

A number of studies have examined the rate of relapse or recurrence in patients who have responded to acute therapy (Table 2). In most studies, patients were required to achieve full remission during acute, open-label treatment to qualify for randomization to the double-blind relapse-prevention phase. In recurrence studies, patients generally must sustain a remission for 6 months before being randomly assigned to receive to the double-blind prevention phase.

SSRIs

Fluoxetine, paroxetine, sertraline and citalopram have demonstrated efficacy in the prevention of relapse. Continuation therapy with fluoxetine significantly decreased relapse rates by about half at 24 and 38 total weeks of therapy compared with placebo.[54] The efficacy of paroxetine in preventing relapse and recurrence was demonstrated in a study of 135 patients who had achieved full remission.[58] Cumulatively, significantly more patients who continued paroxetine therapy remained in remission after 1 year (84%) than those who were switched to placebo (57%). There is also demonstrated efficacy for sertraline in the prevention of recurrence in 161 patients with chronic major or double depression.[59] Over the 76 weeks of follow-up, recurrence was seen in 26% of the sertraline group compared with 50% of the placebo group. In a comparison of fluvoxamine and sertraline maintenance therapy, no significant differences were observed in

Table 2: Rates of relapse and recurrence in recent clinical trials of antidepressant therapy for depression

Study	Pretreatment	Groups to which patients were randomly assigned, n values	No. (and %) of patients who relapsed 3–6 mo after full remission	No. (and %) of patients who relapsed 7–10 mo after full remission	No. (and %) of patients with recurrence of depression after sustained remission for 4–6 mo		Patient types, definitions
Patients in full remission before randomization							
Reimherr et al[54]	12- to 14-wk acute FLX	FLX 20 mg/d, n = 299 Placebo, n = 95	6 mo 78 (26) 46 (48) p < 0.001	9.5 mo 9/105 (9) 12/52 (23) p < 0.04	62 wk 3/28 (11) 5/34 (15) p = ns		Outpatients with depression > 1 mo 86.6% rated as high probability of relapse MDD relapse criteria × 2 wk or HAM-D$_{17}$ > 14 × 3 wk Randomized as follows: FLX 20 mg/d × 14 wk, n = 97 FLX 20 mg/d × 38 wk, n = 100 FLX 20 mg/d × 50 wk, n = 102 Placebo × 50 wk, n = 95
Montgomery and Dunbar[58]	8-wk acute PRX	PRX 20–30 mg, n = 68 Placebo, n = 67	4 mo 2 (3) 13 (19) p < 0.01		12 mo 9/66 (14) 16/54 (30) p < 0.05		Recurrent depression (≥ 2 previous episodes) Relapse: CGI ≤ 4 or decline in CGI ≥ 2 or depressive symptoms ≥ 7 days or investigator opinion to treat Completers and dropouts not reported
Keller et al[59]	12-wk acute SRT (sustained for 4 mo)	SRT 200 mg/d, n = 77 Placebo, n = 84			76 wk 20 (26) 42 (50) p = 0.001		Chronic depression Response: 85% had HAM-D$_{24}$ ≤ 10 Re-emergence of depression by consensus assessment Completers: SRT, n = 35; placebo, n = 24
Franchini et al[60,61]	Remission with antidepressant therapy (sustained for 4 mo)	SRT 100–200 mg/d, n = 32 FLV 200–300 mg/d, n = 32			2 yr 7 (22) 6 (19) p = ns	4 yr 3/22 (14) 5/25 (20) p = ns	Recurrent depression (≥ 1 previous episodes) Remission: HAM-D < 8 Antidepressant therapy (77% tricyclics) Recurrence: clinical worsening, HAM-D > 15 All 64 patients completed study
Robert and Montgomery[62]	8-week CTL	CTL 20–60 mg, n = 152 Placebo, n = 74	6 mo 21 (14) 18 (24) p = 0.04				Patients with depression > 3 mo were excluded Relapse: both MADRS > 25 and clinical judgment of investigator
Entsuah et al[66]	8-wk acute VFX	VFX 75–225 mg/d, n = 161 Placebo, n = 157	6 mo 45 (28) 82 (52) p ≤ 0.05				Recurrent depression Remission: HAM-D$_{21}$ ≤ 10 and CGI ≤ 3 Relapse: CGI > 4 or 2 CGI ≥ 4 or final CGI > 4 for any patient who withdrew for any reason

Table 2 (cont): Rates of relapse and recurrence in recent clinical trials of antidepressant therapy for depression

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Thase et al[68]	8- to 12-wk MTZ	MTZ Placebo n = 156			10 mo 19.7% 43.8% p = ?	Not reported Relapse: 1 HAM-D$_{17}$ > 18 or 2 HAM-D$_{17}$ = 15–17
Patients with a response before randomization						
Lonnqvist et al[65]	6-wk acute therapy	MCL 300–450 mg/d, n = 29 FLX 20–40 mg/d, n = 30	3 mo 2 (7) 1 (3)			66% of patients first depressive episode Response: HAM-D$_{17}$ ≤ 16 Relapse: both HAM-D$_{17}$ > 16 and CGI > 3 Dropouts: MCL, 7/29; FLX, 3/30
Versiani et al[63]	6-wk acute RBX	RBX 8 mg/d, n = 145 Placebo, n = 141	6 mo 52/133 (39) 79/132 (60) p ≤ 0.001		12 mo 9/75 (12) 20/49 (41) p = 0.001	Recurrent MDD Response: > 50% decrease in HAM-D, Remission: HAM-D < 10 (66% of patients) Relapse: > 50% increase in HAM-D or HAM-D$_{21}$ > 18 Dropouts: RBX, 64/143; placebo, 75/140

Note: CGI = Clinical Global Impressions; CTL = citalopram; FLV = fluvoxamine; MADRS = Montgomery–Asberg Depression Rating Scale; MTZ = mirtazapine; NFZ = nefazodone; ns = not significant. See Table 1 footnote for other abbreviations.

cumulative recurrence rates at either the 2-year (about 20%) or 4-year follow-up (about 30%).[60,61] Continuation therapy with citalopram was also found to significantly lower the rate of relapse at 6 months compared with placebo (14% v. 24%, respectively).[62] Relapse rates may have been underestimated in this study, since criteria for relapse were severe and the relapse rate in the placebo group was lower than expected.

Reboxetine

Maintenance therapy with reboxetine (not available in Canada) for the prevention of relapse and recurrence of depression was evaluated in a 1-year study in patients with recurrent major depression.[63] Full remission was defined as a HAM-D ≤ 10 and relapse as a ≥ 50% increase in HAM-D or a HAM-D ≥ 18. Relapse rates during the first 6 months of follow-up among patients who had responded to acute reboxetine therapy were significantly lower with reboxetine than with placebo (39% v. 60%, respectively). Patients who were relapse-free at 6 months remained in the trial for an additional 6 months. During this maintenance phase, 41% of patients in the placebo group compared with only 12% in the reboxetine group had experienced a recurrence at 1 year (p ≤ 0.001). Of the patients (n = 237) who were in full remission at the end of the 6 weeks of initial therapy, 48% of the placebo group compared with only 16% of the reboxetine group had relapsed at 1 year.

Nefazodone

Nefazodone demonstrated prevention of relapse of depression in a 1-year placebo substitution trial.[64] Patients in full remission after 16 weeks of acute nefazodone therapy were randomly assigned to receive either nefazodone (n = 65) or placebo (n = 66) for a further 36 weeks. Remission was defined as a HAM-D$_{17}$ < 10 and relapse as HAM-D$_{17}$ ≥ 18 or discontinuation for lack of efficacy. At 9 months, relapse rates were significantly lower for patients randomly assigned to continue nefazodone treatment than they were for those switched to placebo (1.8% v. 18.3%, respectively, p = 0.009). Relapse rates were 19% with nefazodone and 51% with placebo (p = 0.028) when discontinuations due to lack of efficacy were included.

Moclobemide

In a comparison study, 59 patients who had responded

(i.e., HAM-D ≤ 16) to double-blind treatment with 6 weeks of moclobemide or fluoxetine therapy agreed to continue and were randomly assigned to 12 weeks of continuation therapy with moclobemide or fluoxetine.[65] No significant differences were seen between the groups. Relapse occurred in 2 patients (7%) in the moclobemide group and 1 (3%) in the fluoxetine group, but 23% of patients in the fluoxetine group and 10% in the moclobemide group dropped out of the study.

Venlafaxine

Venlafaxine demonstrated efficacy in the prevention of relapse in a 6-month, double-blind placebo-substitution trial.[66] Patients with recurrent depression who achieved full remission after 8 weeks of acute venlafaxine therapy were randomly assigned to continue venlafaxine ($n = 161$) or switch to placebo ($n = 157$). Remission was defined as a $HAM-D_{21} \le 10$ and Clinical Global Impression Severity of Illness (CGI-S) ≤ 3 and relapse as CGI-S > 4 or 2 consecutive CGI-S ≥ 4 (moderately ill). Cumulative relapse rates at 3 and 6 months were 19% and 28% with venlafaxine compared with 44% and 52% with placebo ($p < 0.001$). When dropouts for unsatisfactory efficacy were included in survival estimates, cumulative probability of continued efficacy was also significantly higher with venlafaxine (74%) than with placebo (50%) ($p = 0.0001$).

Venlafaxine has also demonstrated efficacy as long-term maintenance therapy for the prevention of recurrence of depression.[67] Patients who had a sustained response for at least 6 months during open-label venlafaxine therapy were randomly assigned to either venlafaxine (100–200 mg/d, $n = 106$) or placebo ($n = 107$) for 12 months. Recurrence, defined as CGI-S ≥ 4, HAM-D ≥ 20 or more than 2 HAM-D > 10, occurred in 51% of patients treated with placebo compared with only 20% of patients treated with venlafaxine ($p = 0.0001$). Significantly more patients in the venlafaxine group (50%) than in the placebo group (24%) completed the 1-year double-blind study.

Mirtazapine

Mirtazapine demonstrated efficacy for the prevention of relapse in a 40-week double-blind placebo-substitution trial.[68] Patients who achieved remission after 8–12 weeks of open-label treatment with mirtazapine ($n = 156$) were randomly assigned to continue therapy or switch to placebo. Remission was defined as HAM-D ≤ 7 and relapse as HAM-D ≥ 18 at 1 visit or between 15 and 17 on 2 consecutive visits. Those patients who continued mirtazapine therapy had a significantly lower relapse rate than those in the placebo group (i.e., 20% v. 44%) after approximately 1 year of therapy.

Relapse and recurrence prevention with other strategies

Other antidepressant strategies have also been examined for their potential in preventing relapse or recurrence. Data suggest that lithium augmentation and continuation ECT may also be effective continuation strategies to prevent relapse in patients that respond to these strategies acutely.

Lithium augmentation

Lithium carbonate has been found to be effective in preventing manic recurrences in patients with bipolar disorder, but its effectiveness in combination with antidepressant drugs in preventing depressive disorders is less clear.[69] Lithium augmentation has shown the potential for relapse prevention in a small study in patients with refractory depression. Patients who had responded to acute lithium augmentation during an open 6-week study ($n = 30$) were randomly assigned to placebo or to continue lithium augmentation for an additional 4 months.[70] Antidepressant medication was continued throughout the study, with no significant differences between the 2 groups. Relapses (including 1 suicide) occurred in 7 (47%) of the 15 patients in the placebo group and none of the 14 patients who received lithium augmentation.

However, in a seminal study almost 2 decades earlier, lithium augmentation of antidepressant therapy was reported to be no more effective than antidepressant alone for preventing recurrences. One hundred and fifty patients, who were controlled on the combination of imipramine and lithium carbonate, were randomly assigned to receive either imipramine or lithium carbonate alone, the combination of lithium carbonate and imipramine, or placebo.[71] Recurrence of depression occurred in 26% of patients who were taking the combination, 33% taking imipramine alone, 57% taking lithium alone, and 65% of those in the placebo group. However, the treatment effects were significantly related to the severity of the index episode. Also, only

36% of the patients with unipolar depression were judged to be treatment successes in this study.

Electroconvulsive therapy

ECT is an effective antidepressant in the acute, short-term treatment of depression, but its role as continuation or maintenance therapy has been underinvestigated. Continuation ECT (C-ECT) was found to exhibit a sustained prophylactic effect for a year after the index episode in a retrospective review of 33 courses of C-ECT in patients with affective illnesses conducted from an inpatient service between 1985 and 1991.[72] The mean intertreatment interval was 10 days, and the average duration of treatment was 10 weeks. The rate of relapse with C-ECT was 33% over 1 year; this was 42% lower than the 95% relapse rate reported for patients maintained on continuation pharmacotherapy before the C-ECT program started. However, in a trial comparing pharmacotherapy or placebo continuation after ECT, at 6-month follow-up, relapse occurred in 65% of the placebo-treated patients, compared with 30% of the imipramine-treated patients and 10% of the paroxetine-treated patients.[73]

Similar long-term benefits were found in another retrospective, case-controlled study comparing C-ECT with antidepressant therapy to antidepressant therapy alone in patients with a positive response to acute ECT.[74] The cumulative probability of continued effectiveness was significantly better with C-ECT compared with antidepressants alone at both 2 years (93% v. 52%, respectively) and 5 years (73% v. 18%, respectively).

Summary

There is evidence that full remission should be the goal of antidepressant therapy; patients with residual symptoms are at an increased risk of relapse and recurrence. Given that the greatest chance of achieving full remission occurs early in the course of treatment, initial antidepressant strategies should be those that have the greatest therapeutic potential.

In patients who achieve full remission, continued antidepressant therapy has clearly been shown to reduce the probability of relapse and recurrence by about half compared with placebo. Therefore, once a patient achieves remission, it is important to continue the same antidepressant for at least 6–12 months, and considerably longer for many patients, to prevent relapse or recur-

rence. Medication should continue at the dose that was initially effective because using low-dose maintenance therapy appears to decrease the protective benefits.

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