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ORIGINAL ARTICLE

Guidelines in major depressive disorder, and their limitations

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Abstract
Depression is a highly disabling, recurrent disease that imposes a significant burden on the individual, their close contacts, and on society. Despite the existence of treatment guidelines for major depression, management frequently falls short of these recommendations, sometimes due to inadequate doses or duration of prescribed antidepressant medication; at other times secondary to patient non-adherence to the recommended treatment. Evidence-based treatment guidelines developed by the major mental health organizations advise that patients who have experienced either a first or a recurrent episode of major depression should receive continued therapeutic doses of medication for at least 4–6 months following symptom remission, to reduce the risk of relapse. Further to this, antidepressant prophylaxis is beneficial in any patient with a history of three or more major depressive episodes, or two or more episodes in the last 5 years. Selective serotonin reuptake inhibitors (SSRIs) have demonstrated excellent efficacy and tolerability in the treatment and prophylaxis of major depression, as well as being associated with significant reduction in suicide risk in some populations. Escitalopram, an atypical SSRI that has shown superiority to conventional SSRIs and venlafaxine in clinical studies, has demonstrated particular benefits in severely depressed patients, in whom its efficacy appears to increase with increasing severity of depression. In the absence of formal treatment guidelines for severe depression, or comborbid depression and anxiety, escitalopram appears to be a logical treatment choice.

Key Words: *Depression, guidelines, treatment, SSRIs, escitalopram, suicide*

Introduction

Depression is a widely prevalent, chronic and highly disabling disorder that places a substantial burden on the affected individual, their immediate family and caregivers, and on society as a whole. At the individual level, depression not only inflicts profound distress, but also reduces lifespan by approximately 10 years [1]. Further to this, depression is a negative prognostic indicator for morbidity and mortality in patients with concurrent medical disorders, as was demonstrated in a prospective study of >6500 individuals in whom depressive symptoms at baseline predicted increased stroke mortality (hazard ratio 1.66; $P<0.006$) following non-fatal stroke [2]. Depression is also associated with a heavy non-fatal burden at both individual and population levels. In the year 2000, major depression accounted for almost 12% of all years lived with disability worldwide [3].

The costs to society include those of reduced work productivity, as well as increased use of medical services. Across Europe, individuals with depression are absent from work an average of 9–12 days per year, compared with only 2–3 days in their non-depressed counterparts [4]. Calculations of the economic consequences of depression in the United States indicate that $16–17 billion were lost as a result of depression in 1990 [5].

The overall impairment caused by depression can be estimated using Disability Adjusted Life Years (DALYs), a measure of the sum of years lost due to premature mortality and disability, adjusted for severity [6]. Using this tool, depression is predicted to be the second leading cause of disability worldwide by 2020, second only to ischemic heart disease [7].

Despite this profound burden, much of which can be alleviated by appropriate treatment, depression remains under-diagnosed and under-treated. The goals of this paper are (1) to underscore the importance of recognizing depression as one of the major public health problems of our time, (2) to examine whether existing treatment guidelines offer the breadth and depth to provide clinicians with sufficient guidance to ensure the most favorable patient outcomes, and (3) to identify patient subgroups for whom guidelines are lacking, and propose

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treatment for such patients based on the clinical trial data available.

Current evidence-based treatment guidelines

The discipline of evidence-based medicine – defined as the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients – was developed to guide healthcare practitioners in applying high-quality evidence to clinical diagnostics and decision-making. However, in many cases, the evidence on which treatment guidelines for depression are based is insufficient to offer detailed guidance on the management of individual patients, many of whom do not fit into distinct, easily classifiable categories.

Current guidelines for the management of depression are based on the widely accepted concept of depression as a disorder with an acute phase which, if adequately treated, responds with improvement in symptoms to the point of remission – a state defined by relative normalcy of emotional and psychological well-being. After attainment of remission, continuation therapy is necessary to maintain improvement, achieve recovery and avoid relapse. If depression emerges 6 months or more later, this is considered a new, recurrent episode [8].

The available evidence indicates that continuation therapy should be maintained for at least 4–6 months after full symptom remission in individuals with first or recurrent episodes of major depression [9–15], in order to reduce the risk of relapse. Failure to continue treatment and consolidate remission results in relapse in 50% of patients, with particular hazard 2–3 months after stopping treatment [12]. The SSRIs, including escitalopram, citalopram, paroxetine, sertraline and fluoxetine, all demonstrate efficacy in preventing depressive relapse when taken for 4–6 months [12,16–20]; premature discontinuation significantly increases the relapse rate. Given their proven efficacy, good tolerability profile, and relative safety in overdose, selective serotonin reuptake inhibitors (SSRIs) are commonly considered first-line therapy in major depression.

Clinical practice falls short of current guidelines

Adequate delivery of care relies on aspects of physician prescribing, as well as patient adherence to the prescribed treatment. In a recent study investigating the association between the appropriate use of treatment guidelines and the incidence of relapse, <30% of patients were treated in accordance with the available guidelines, and 24% of these patients experienced depressive relapse or recurrence [21]. Of those who did receive adequate therapy, 22% relapsed, compared with 50% receiving placebo.

Despite clear guidelines stipulating that 4–6 months of continued treatment is necessary after achieving remission, duration of treatment remains inadequate in a disturbing proportion of cases. In a patient record linkage study in Scotland in 1996, as many as 58% of patients received prescriptions for < 60 days of treatment, and 68% were treated for <90 days [22].

Discouragingly, prescribed doses also fall below recommended therapeutic levels in many cases. In one primary care survey in the UK in 1996, which included over 1.5 million patients and over 80,000 prescriptions, almost 60% of patients received prescriptions for sub-therapeutic doses of TCAs [23], although doses of SSRIs were almost universally within the recommended range. Now that newer agents, including SSRIs, are prescribed more frequently than TCAs, and the starting dose of SSRIs is effective, it is likely that increasing numbers of patients will receive therapeutic drug doses.

The extent to which patients fail to assume responsibility for satisfactory treatment is also of concern. Physicians rely on patients to fill prescriptions, continue treatment and discuss difficulties with adhering to therapy in a timely manner. However, surveys of patient behavior indicate that 30% of patients do not fill their first prescription; up to one-third discontinue treatment within 1 month, and over 40% have discontinued within 3 months [24–26]. Perhaps unsurprisingly, most of these patients did not inform their physician that they were no longer taking their medication. Unfortunately, this situation has not improved in the last decade.

Depression is a highly recurrent disorder that warrants antidepressant prophylaxis

The deficiencies in delivery of care outlined above are particularly disappointing, given that depression is highly recurrent and widely available antidepressants have demonstrated excellent prophylactic and treatment efficacy. Data show that individuals who experience a first episode of depression have a 28% risk of recurrence within 1 year [8]; this risk increases to 90% in individuals who have had three previous depressive episodes [27–29]. The strong tendency for depression to recur was elegantly estimated using data from a long-term observational study of approximately 360 patients with major depression, in whom it was calculated that 62% of patients with a first depressive episode experienced a further episode within 5 years, rising to a total of 87% at 15 years [28]. Such striking statistics compel us to use the available drugs appropriately, in order to prevent recurrent depressive episodes.

Prophylactic antidepressant therapy is indicated in any individual with known recurrent or chronic depression. Guidelines indicate that prophylaxis is

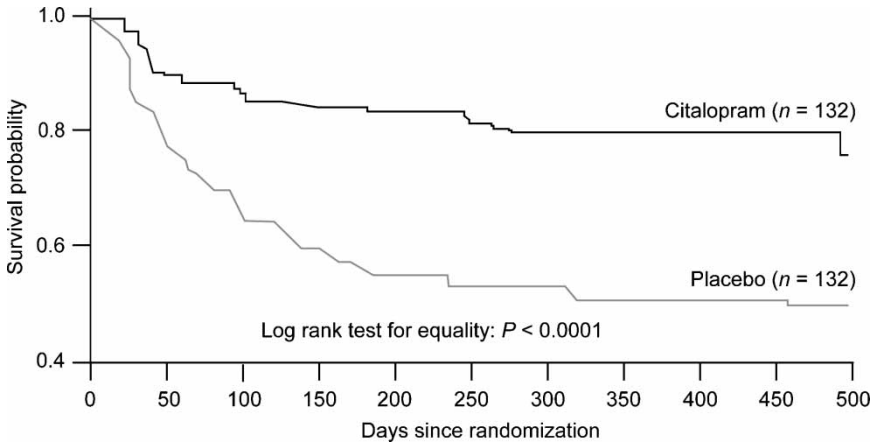

Figure 1. In a study comparing citalopram (20, 40 or 60 mg daily) versus placebo, prophylactic maintenance therapy with citalopram resulted in a significantly longer time to recurrence ($P < 0.0001$). The figure was truncated at 500 days due to the low numbers of patients remaining in the study. Reprinted with permission from [33], copyright of the Royal College of Psychiatrists.

beneficial in any patient with a history of three or more depressive episodes, or two or more episodes in the last 5 years [30,31], and that treatment should probably continue indefinitely.

The SSRIs also demonstrate proven effectiveness in preventing depressive recurrence when administered over 1–2 years [18,31–33]. In a three-period study comparing citalopram (20, 40 or 60 mg daily) versus placebo, 427 patients with recurrent unipolar depression received open-label treatment for 6–9 weeks; responders received a further 16 weeks treatment to consolidate remission, followed by randomization to double-blind prophylactic citalopram or placebo therapy for a further 48–77 weeks. Citalopram-treated patients had a significantly longer time to recurrence ($P < 0.0001$) (Figure 1). Although the study was not powered for subgroup analysis, time to recurrence was statistically significantly longer in all citalopram dose groups compared with placebo.

Antidepressant use reduces suicide risk

The topical and controversial relationship between antidepressant use and suicidality continues to fuel professional and media debate. The troubling assertion that SSRIs may themselves increase suicide attempts was recently refuted by a large meta-analysis that included both published and unpublished regulatory data from 477 randomized controlled trials of SSRIs versus placebo, including over 40,000 adults [34]. Despite being insufficiently powered to detect clinically significant risks or benefits – such a study would require data from approximately 2 million individuals – and only including trials of short mean duration (<10 weeks), this sizeable analysis concluded that there was no evidence that SSRIs increase suicide risk, and the odds ratio in fact suggested a protective effect of SSRIs, albeit non-significantly (odds ratio = 0.85; 95% credible interval 0.20–3.40).

Extensive data strongly indicate that treatment of depression with effective antidepressants reduces the rate of completed suicides in a statistically significant manner. Data drawn from a large Swedish registry showed that in 1996 only 20% of individuals with diagnosed depression were receiving antidepressants; the suicide rate in untreated individuals was almost double (1.8 times greater) that in treated patients (141 vs. 259 suicides per 100,000 person years) [35].

The mortality benefit of treating depressed patients is strongly supported by data from a long-term prospective study of 406 patients with severe unipolar ($n = 186$) or bipolar ($n = 220$) depression, 76% of whom were followed up over 34–38 years, until their deaths [36], with analysis of survivor data continuing until 2003 (Figure 2). Patients with unipolar depression who received long-term antidepressant treatment (at least 6 months treatment after remission) had a 2.5-fold lower suicide rate than untreated patients (standardized suicide mortality rate (SMR) = 11.9 vs. 38.1; $P < 0.001$), even though treated patients were more severely depressed. The most recent mortality analysis of this same patient group in 2005 [1] continued to support the survival advantages of antidepressant treatment: SMR and suicide rates in non-treated patients were 33.3 and 21.2%, respectively, compared with 13.8 and 10.0% in treated individuals ($P < 0.05$ and $P = 0.09$ for SMR and suicide rate, respectively). Consistent with the medical literature, a history of suicide attempts was a significant predictive factor for completed suicide. These data strongly suggest a protective effect of antidepressant treatment on the suicide rate.

Investigating the decline in suicide rate that has paralleled increasing antidepressant use in adolescents, an analysis of prescription data from the largest pharmacy benefit management organization in the United States compared regional suicide rate against the number of filled antidepressant prescriptions over the 10-year period from 1990 to 2000, in

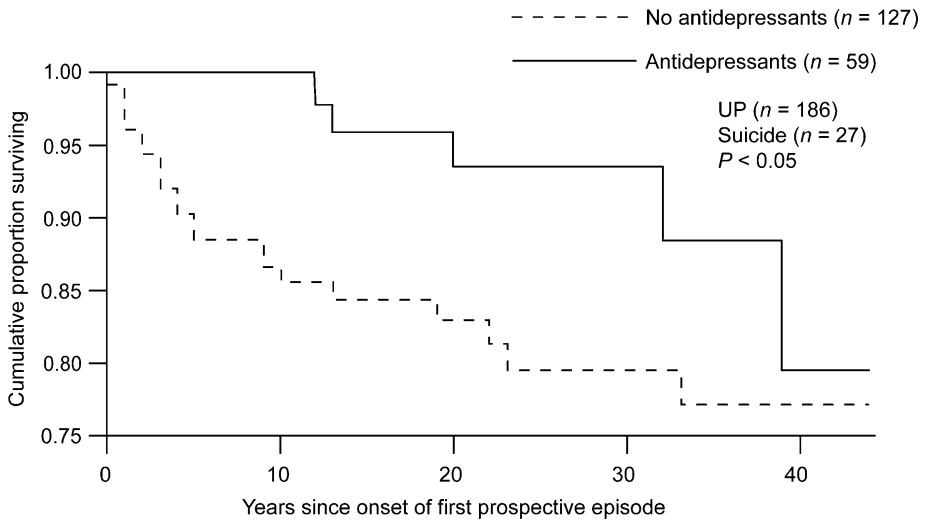

Figure 2. In a study of 186 hospitalized patients with severe unipolar depression, followed up over nearly 45 years, individuals who received long-term antidepressant treatment (at least 6 months treatment after remission) had a significant survival advantage compared with untreated patients ($P < 0.05$). Reprinted with permission from [1], copyright of Taylor and Francis.

males and females aged 10–19 years [37]. Investigators found that a 1% increase in antidepressant use was associated with a decrease of 0.23 suicides per 100,000 adolescents per year ($P < 0.001$ for the association between suicide and antidepressants), with particular advantage in older, male adolescents and those from low income regions. This apparently protective effect applied to SSRIs but not TCAs.

From the evidence available to date, the only intervention proven to reduce suicide risk is improved diagnosis and treatment of depression using adequate doses of antidepressants, for a sufficient length of time. Only by implementing effective diagnosis and treatment can we claim to offer an acceptable standard of care.

The need for expanded guidelines

Despite the availability of clear treatment guidelines for many categories of patient, there remain noteworthy gaps for certain patient groups. Among those remaining in need of guidelines are patients with severe depression or with comorbid depression and anxiety.

Severe depression

While definitions of severe depression vary, an operational definition in clinical practice usually includes a combination of overall symptomatology, scores on severity rating scales, and degree of functional impairment [38]. Data from some studies in hospitalized patients with severe depression have demonstrated that the TCA clomipramine was superior to the SSRIs citalopram and paroxetine [39,40]. By extension, such data suggest that conventional SSRIs, which are selective for serotonin alone, may not have sufficient efficacy in severe depression. This hypothesis that dual action is more effective is supported by data comparing venlafaxine – a noradrenergic and serotonergic agent – with fluoxetine: after 4 and 6 weeks of treatment, venlafaxine (200 mg daily) demonstrated a clear advantage over fluoxetine (40 mg daily) in a head-to-head trial in 68 severely depressed inpatients ($P \leq 0.05$ on MADRS and HAM-D rating scales) [41]. Interestingly however, in a head-to-head comparison between the dual serotonin action SSRI escitalopram and venlafaxine XR, an 8-week randomized, double-blind, highest-recommended-dose study concluded that a significantly greater percentage of severely depressed patients (MADRS > 30) taking escitalopram 20 mg/day achieved remission (MADRS score ≤ 12) (50.5%) at 8 weeks, compared with those taking venlafaxine XR 225 mg/day (41.8%; $P < 0.05$) [42].

One of the most intriguing findings to emerge during comparative analysis of the SSRIs is the distinct, potentially unique action profile of escitalopram, the *S*-enantiomer of citalopram, in severely depressed patients. In contrast to the racemic compound, citalopram, escitalopram shows increasing antidepressant efficacy with increasing severity of depression. A very similar pattern of increasing efficacy with increasing severity of depression was demonstrated for escitalopram (20 mg daily) when it was compared against paroxetine (40 mg daily) [43].

Examination of pooled data from 10 randomized, double-blind trials that compared escitalopram against an active comparator (another SSRI or venlafaxine) in major depressive disorder, further highlighted the superiority of escitalopram in severe depression [44]. In this meta-analysis that included data from > 2600 patients (escitalopram: $n = 1345$; SSRIs: $n = 1102$; venlafaxine XR: $n = 240$), escitalopram demonstrated greater antidepressant efficacy than its comparators [MADRS total score was 1.07 points lower than that of the pooled comparators at

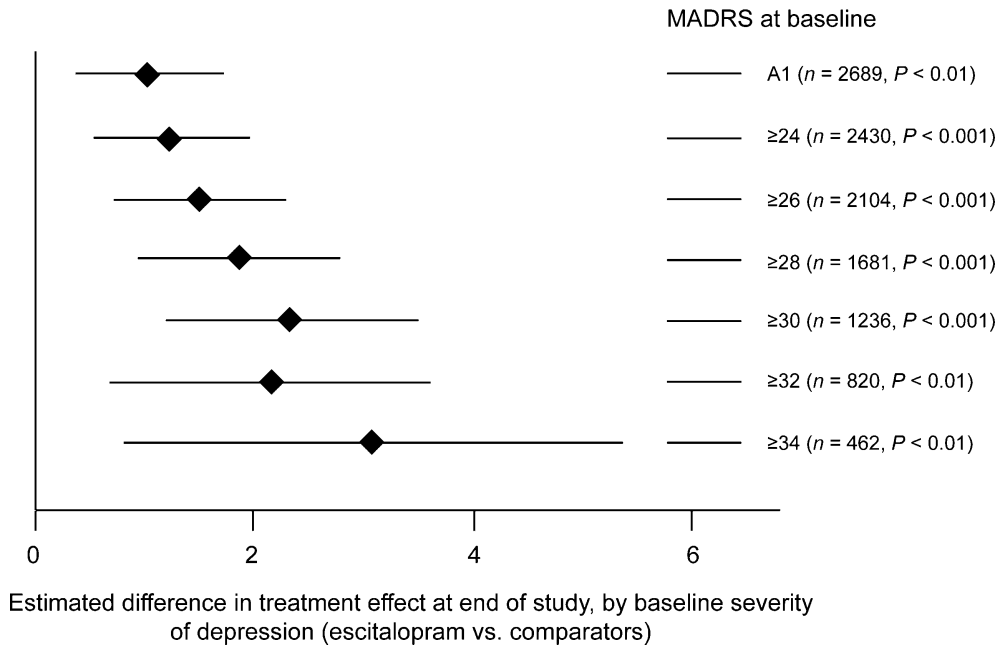

Figure 3. A meta-analysis that compared escitalopram against pooled data from other SSRIs and venlafaxine XR in 2687 patients found that the superior efficacy of escitalopram in severely depressed patients increased with increasing severity of depression. Reprinted with permission from [44], copyright of the Canadian Medical Association.

study endpoint ([95% CI]: 0.42–1.73; $P < 0.01$)], as well as greater response (odds ratio = 1.29; [CI]: 1.07–1.56; $P < 0.01$) and remission rates (odds ratio = 1.21; [CI]: 1.01–1.46; $P < 0.05$). A similar efficacy advantage for escitalopram was observed in the subgroup of severely depressed individuals, in whom escitalopram patients achieved a 2.34-point lower MADRS score ([CI]: 1.22–3.47; $P < 0.001$) at study endpoint. It is noteworthy that the more severe the depression at baseline, the more striking the discrepancy between escitalopram and its comparators (Figure 3). Furthermore, the difference in response and remission rates was also significantly in favor of escitalopram in the severely depressed subgroup [45]. It is hoped that these findings will be considered during development of guidelines that address treatment of severe depression.

A plausible explanation for the superior efficacy observed with escitalopram compared with the conventional SSRIs, particularly in severely depressed individuals, is the presence of a secondary allosteric binding site that may enhance the affinity of ligands bound at the high-affinity primary serotonin transporter site [45–47]. Allosteric binding may also potentiate escitalopram's antidepressant effect, which probably occurs as a result of the prolonged inhibition of serotonin and higher extracellular serotonin levels that follow a reduction in the rate of dissociation from the serotonin transporter [45]. While it has been proposed that the superiority of venlafaxine over conventional SSRIs relates to the dual uptake inhibition of noradrenaline and serotonin, this allosteric binding hypothesis may go some way toward explaining the added efficacy advantage of escitalopram over other antidepressants in the treatment of severe depression.

Comorbid anxiety and depression

The majority of clinical trials in depression exclude patients with comorbid disorders, making development of evidence-based guidelines for this patient subgroup particularly difficult. However, in the absence of formal treatment guidelines it seems logical to treat major depression according to existing recommendations using SSRIs as first-line treatment, since SSRIs have also demonstrated clearcut efficacy in treating anxiety disorders.

Conclusions

In order to offer the highest standard of care to patients with depression, both physicians and patients must adhere to existing, published treatment guidelines. Achieving this goal will probably require supplementary targeted education for patients, primary care and specialist physicians. SSRIs remain the first-line therapy for prophylaxis and treatment of major depression; among them, escitalopram appears to have a unique mode of action that may explain its superior efficacy when compared with conventional SSRIs and venlafaxine in severe depression, and its ability to increase its treatment effect with increasing severity of depression. We remain in need of evidence-based treatment guidelines for patients with severe depression, comorbid anxiety and depression, and those with depression and concurrent medical disorders.

Key points

- Depression is a highly disabling, recurrent disease that imposes a significant burden on the individual, their close contacts, and on society
- Guidelines recommend that all patients should receive treatment for at least 4–6 months after remission, to reduce the risk of relapse. Antidepressant prophylaxis is beneficial in any patient with three or more depressive episodes, or two or more episodes in the last 5 years
- SSRIs are the treatment of choice for treatment and prophylaxis in major depression
- Treatment guidelines are lacking for severe and comorbid depression, but evidence from randomized clinical trials indicates that escitalopram is superior to conventional SSRIs and venlafaxine in severe depression
- The only strategy proven to reduce suicide risk is improved diagnosis and treatment of depression using adequate doses of antidepressants, for a sufficient length of time

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