Optimising antidepressant use in clinical practice: towards criteria for antidepressant selection

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Background Current treatment for depression in primary care and other out-patient settings demonstrates a pattern that is incongruous with the magnitude of the burden of depression suggested by its associated disability.

Aims To review important considerations in current depression treatment with a focus on antidepressant use.

Method Factors influencing the undertreatment of depression in real-world settings are examined.

Results Patient and clinician behaviour as well as the incentives created by the health care system affect the likelihood of realising effective antidepressant therapy in practice.

Conclusions Given the complexities of clinical practice, selection criteria for an antidepressant should include safety, efficacy and tolerability, as well as the ability of the antidepressant to deliver real-world efficacy while balancing health care costs in the long term.

Declaration of interest J. M. received an honorarium and travel expenses from Eli Lilly & Co.

Depression is a growing burden, in terms of both economics and quality of life, for patients, families, employers and payers worldwide (Wells *et al*, 1989*a*; Greenberg *et al*, 1993*a*; Kind & Sorenson, 1993). Current projections indicate that the global burden of depression will rank second only to that of ischaemic heart disease by the year 2020 (Murray & Lopez, 1996). The current costs of depression are comparable (although differently distributed) to those of other major illnesses, such as cancer, AIDS and coronary heart disease (Greenberg *et al*, 1993*b*). However, the costs associated with depression are largely indirect and are therefore less obvious than those associated with other chronic illnesses. These indirect costs include productivity losses caused by absenteeism and sub-optimal performance at work (Greenberg *et al*, 1993*b*). Additionally, depression is usually characterised by repeated relapse or recurrent episodes (Prien & Kupfer, 1986). This chronicity magnifies depression's long-term societal impact and economic burden.

Despite this significant personal, societal and economic impact, treatment patterns for depression in primary care and other out-patient clinical settings are incongruous with the magnitude of the disease burden and disability. A number of factors such as patient attitudes, rates of diagnosis, inadequate antidepressant prescribing and limited health insurance coverage contribute to this undertreatment. For example, it is suggested that just one-third of people with depression explicitly seek treatment for their illness (Shapiro *et al*, 1984; Lepine *et al*, 1997). Furthermore, only about half of patients with major depression who are seeking primary care for any reason are recognised by their physicians as having a psychosocial problem, and less than half of these are explicitly recognised as being depressed (Lepine *et al*, 1997). It has been optimistically estimated that, in general medical settings, two-thirds of depressed patients are actually identified by practitioners as being psychologically distressed, and of these patients, slightly more than half are prescribed antidepressant medication (Wells *et al*, 1989*b*; Simon *et al*, 1995).

When patients are treated for depression in primary care or another out-patient setting, they receive pharmaceuticals about 75% of the time. Clinical trials of antidepressants suggest an efficacy rate approaching 80% (Anderson & Tomenson, 1994). However, in terms of criteria for adequate dose and duration of treatment, only about 25% of patients in clinical practice are adequately treated when they are prescribed antidepressants (Katon *et al*, 1992; Lepine *et al*, 1997), even with the better-tolerated selective serotonin reuptake inhibitors (SSRIs) (Dunn *et al*, 1998). Thus, the promise of effective treatment implied by clinical trial efficacy rates for antidepressants is not realised in clinical practice owing to a variety of complex interactions between patient, provider and health-system characteristics. This situation in primary care and other out-patient clinic settings improved gradually over the 1990s but remains sub-optimal in most health care delivery systems.

ANTIDEPRESSANT THERAPY

The goals of antidepressant therapy of depression are well known: removal of symptoms, restoration of patient functioning and prevention of relapse or recurrent episodes. Consensus guidelines have been issued by the British Association for Psychopharmacology (1993) and the Royal College of Psychiatrists (1992) for the management of depression with antidepressants. These guidelines recommend that for treatment to be effective, antidepressants should be prescribed at a dose shown by clinical trials to be effective in treating depression, and continued for at least 4 months beyond initial symptom resolution (with a longer duration for subsequent episodes). These guidelines are broadly consistent with other consensus groups' recommendations (World Health Organization Mental Health Collaborating Centers, 1989; Agency for Health Care Policy Research, 1993). In addition to antidepressant therapy with adequate provider follow-up, accurate diagnosis, practical support and problem-solving techniques are important elements in primary care management of patients with depression.

https://doi.org/10.1192/bjp.179.42.s1 Published online by Cambridge University Press

The advent of better-tolerated antidepressants (beginning with the SSRIs and other new drugs) and the initiation of numerous educational programmes to increase the awareness of the burden of depression (Priest, 1994; Paykel *et al*, 1997) had the potential to improve antidepressant prescribing. Sadly, the evidence from clinical practice still shows that few patients receive an adequate dose or duration of antidepressant therapy (Donoghue & Tylee, 1996; Katzelnick *et al*, 1996; MacDonald, 1997; Rosholm *et al*, 1997; Donoghue, 1998; Dunn *et al*, 1998; Gregor *et al*, 1998). This suggests that while broadly based educational awareness policies and innovative drugs are necessary, they are not sufficient for improving antidepressant prescribing. Because many factors influence antidepressant prescribing, no single approach is likely to be sufficient to optimise depression treatment.

Many factors influence the effectiveness of antidepressant use in clinical practice, including the illness itself, pharmacological features of specific antidepressants (such as side-effects and dosing regimens) and individual behaviour (Demyttenaere, 1998). At a basic level, people with depression may not seek help for their mood disorder symptoms, focusing instead on somatic concerns such as gastrointestinal complaints, fatigue or headaches. Some people may refuse to pursue treatment because of the stigma attached to a mental diagnosis or because they believe they should be able to 'handle it' on their own. Another reason for underdiagnosis of depression by providers is the fear of alienating patients by suggesting that they have symptoms of depression. Finally, many general practitioners lack the time that is required to assess depression; when providers do identify the need for psychiatric evaluation, their patients may be reluctant to follow through on referrals.

Additional factors emerge once a patient is prescribed an antidepressant. These factors include inadequate dose and duration of therapy, as well as compliance issues. Indeed, taking medication in accordance with the prescription's instructions is perhaps the single most important determinant in translating a drug's efficacy demonstrated in controlled clinical trials into its effectiveness in clinical practice. Between 30% and 60% of patients do not take their medications as prescribed (Cramer, 1995; Demyttenaere, 1997). While reasons for this include pharmacological factors such as side-effects or adverse events, compliance is affected particularly by the beliefs and behaviour of both patients and prescribers. For example, patients may feel guilty about taking the medication, or even that they are undeserving of it. They may sometimes believe they do not need the medication once they begin to feel better. Patients taking psychotropic medications such as antidepressants may worry that continuing the medication could result in a drug dependency (Priest *et al*, 1996) or a loss in its effectiveness (Donovan & Blake, 1992). The social stigma attached to mental disorders and associated pharmacological treatments may also inhibit patients' intake of their medications (Fawcett, 1995). Prescribers can undermine compliance by advising 'drug holidays' to minimise side-effects such as sexual dysfunction, even though this practice is not recommended (Demyttenaere, 1997).

At the system level, a primary reason for sub-optimal treatment of depression is the lack of adequate health insurance coverage for long-term psychopharmacological management and other services by mental health professionals. The influence of health care financing arrangements has made it less attractive for providers from different specialities (for example a primary care physician and a psychiatrist) to collaborate, although such an approach shows promise for the treatment of depression (Katon *et al*, 1995). Managed care organisations or other insurance arrangements that exert control over which pharmaceuticals are listed in their formularies or are available to prescribers limit the availability of a wide range of antidepressant treatment options for providers and plan members. Finally, a narrow focus on containing direct health care costs, even when the societal benefits of treatment are great, leads to the promotion of shorter-term interventions that do not address the chronic and recurrent nature of depression.

ANTIDEPRESSANT SELECTION CRITERIA

One approach to improve the selection of an antidepression agent at the individual prescriber level may be for the prescriber to systematically consider five characteristics of the drug: efficacy, safety, tolerability, real-world efficacy and economic value. The first three characteristics are traditional criteria used in selecting an antidepressant. The latter two are important in light of how people actually behave and reflect growing concerns about costs.

An antidepressant's real-world efficacy is determined by (a) its efficacy as demonstrated in controlled clinical trials and (b) how it is used in actual clinical practice. Factors that may influence how an antidepressant is used in the real-world include need for titration, ease of use, frequency of dosing, compliance, medication availability, insurance coverage, length of treatment, prior experience with specific drugs or drug classes, and side-effects. Antidepressants that are effective both in the acute phase and in the long term despite the shortcomings of how they are actually prescribed by providers and used by patients may offer important clinical advantages.

The economic value of antidepressant medications is also an important consideration in the light of increasing concerns about rising health care costs and limited budgets. A drug's economic value is not an innate characteristic of that drug, but is the result of a complex interaction between the patient, the provider and the health care system. Economic comparison studies of antidepressants using data from clinical practice provide a measure of economic value within this context.

When comparing the costs of antidepressant pharmacotherapy, it is important to look at the *total* direct health care costs, not just the drug acquisition cost or even depression-related costs. While depression treatment increases expenditure, it could also reduce overall health care resource utilisation in at least two ways. First, depression is often associated with comorbid illnesses (Agency for Health Care Policy Research, 1993). If depression treatment leads to an improvement in comorbidities, resource utilisation for those disorders may decrease. Second, depression leads to greater reporting of somatic symptoms (Simon & Von Korff, 1991; Kroenke *et al*, 1994). Improvement of the depression might reduce the somatic complaints and also their associated resource use. Thus, it is important for both prescribers and payers to consider the total direct health care expenditure (both depression- and non-depression-related) when assessing the impact of alternative treatment options.

CONCLUSION

Including the five criteria of efficacy, safety, tolerability, real-world efficacy and economic value, along with the individual patient's current symptom profile and other medical history, in deciding which

https://doi.org/10.1192/bjp.179.42.s1 Published online by Cambridge University Press

antidepressant drug to select can help to realise in clinical practice the value of antidepressants as demonstrated in clinical trials, while at the same time balancing health care costs.

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https://doi.org/10.1192/bjp.179.42.s1 Published online by Cambridge University Press