Maximizing treatment outcomes in the depressed patient

Depression is a serious illness associated with morbidity and mortality, but it is treatable. However, outcomes are often far from ideal with patients left with residual symptoms of depression. These are associated with poor social functioning and an increased risk of relapse.

Depression is a terminal, but treatable, illness. It is estimated that in 2000 alone there were 2615 deaths related to depressive illnesses resulting from suicide and accidental poisoning (Thomas and Morris, 2003). This is an underestimate because it only considered deaths registered as suicide by the coroner. Further this estimate does not take into account the increase in mortality caused by depression from physical health conditions such as ischaemic heart disease (Hemingway and Marmot, 1999). Indeed the risk of a myocardial infarction is independently increased four-fold by depression, a similar effect to an individual smoking 20 cigarettes a day (Pratt et al, 1996).

Even in the absence of mortality, depression has a huge negative impact on quality of life and productivity. As a result of its high prevalence (at least one in six adults meeting the criteria for a major depressive episode at some time in their life; Alonso et al, 2004) and associated morbidity and mortality, depression is estimated to cost the UK economy over £9 billion per year in direct and indirect costs (Thomas and Morris, 2003) and to rank as the fourth leading cause of disability in the world (Murray and Lopez, 1996).

Early identification and treatment is important since duration of untreated depression correlates with the likelihood of non-response and the development of chronic depression (Keller et al, 1992). The most commonly used intervention for patients with moderate to severe depression is pharmacotherapy. Guidelines recommend that an antidepressant should be taken for 6 months following full remission of symptoms (McAllister-Williams, 2006). However, a World Health Organization study has shown that the mean duration of prescribed treatment is only 11 weeks with one quarter of patients only treated for 1 month (Goldberg et al, 1998). In addition, up to 30% of patients stop antidepressants within the first month of treatment and up to 50% during long-term treatment (Lingam and Scott, 2002). This relates to many factors including lack of efficacy and intolerance. Side effects of dry mouth, blurred vision, constipation and urinary retention, seen with the tricyclic antidepressants, have been replaced by high rates of nausea, sexual dysfunction and weight gain with new generation antidepressants.

When taken, antidepressant drugs do have established efficacy *vs* placebo in clinical trials, although only 55–70% experience a response to treatment defined as a 50% decrease in symptoms (Fawcett and Barkin, 1997). Indeed, in a 'naturalistic' study in the USA of nearly 3000 patients being managed according to a defined treatment algorithm, only 28% of patients attained full remission of symptoms with first-line treatment (Trivedi et al, 2006). There is clearly a massive need for treatments that are not only well tolerated but also have greater efficacy in a larger proportion of patients.

Partial remission

The condition of 'partial remission', when a patient has shown a 'response' (>50% decrease in symptoms) but has not attained full 'remission' (effectively full resolution of symptoms), is often difficult to treat, especially when established. Cognitive behavioural therapy (CBT) has been shown to be of benefit when added to antidepressant treatment (Paykel et al, 1999), but is a scarce resource. Psychopharmacological strategies, including optimization, switching, augmentation or antidepressant combination, are often of limited utility (Boulenger, 2004). Over 30% of patients, even when actively followed up and managed with a four-step treatment algorithm, fail to reach remission (Rush et al, 2006). A significant proportion of the health-care and socioeconomic cost of depression arises from problems associated with partial remission.

Residual symptoms adversely affect the quality of life of both the patients and their families, being associated with poor physical and social functioning (Judd et al, 2000), and are associated with higher risk of mortality from suicide and physical co-morbidity (Tranter et al, 2002). In addition, compared with patients who achieve full remission, patients with residual symptoms relapse more quickly, have more recurrences, shorter 'well' intervals and are more likely to develop a chronic illness (Boulenger, 2004; Kennedy and Foy, 2005).

Some depressive symptoms appear to be more resistant to treatment than others. These include anxiety, poor

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sleep, fatigue and pain (Hybels et al, 2005; Baldwin and Papakostas, 2006). The nature of residual symptoms appears to be relatively independent of treatment used. For example the rates of residual insomnia are similar after both CBT and pharmacotherapy (Carney et al, 2007) and symptoms are similar after treatment with an selective serotonin-reuptake inhibitor (SSRI) and a noradrenaline-reuptake inhibitor (reboxetine) (Nelson et al, 2005), although it is possible that some antidepressants may be associated with differences (Papakostas et al, 2006).

Different residual symptoms may lead to specific problems in the management of depressed patients. For example individuals with persistent sleep disturbance like insomnia are 40 times more likely to develop a full-blown episode of depression within a year compared to individuals without insomnia (Ford and Kamerow, 1989). The presence of insomnia is also believed to increase the risk of suicide in depressed individuals, while early relief may improve concordance with treatment, and hence improve outcome (Thase, 1999). Painful symptoms are four times more common in depressed than non-depressed individuals (Ohayon and Schatzberg, 2003) and over 90% of patients with residual symptoms have been reported to have some somatic complaint, including pain (Paykel et al, 1995). The presence of significant pain along with depression can lead to a four-fold decrease in the chances of a patient responding to an SSRI (Bair et al, 2004).

Management of depression

It is clear that a multifaceted approach is required to improve outcomes of depressed patients. In England and Wales this is laid out in the National Institute for Health and Clinical Excellence (NICE) guidelines (2004) based on a 'stepped care' approach with five levels. Patients move to, or enter at, higher steps with increasing severity of illness and increased risk. These are briefly described below (see McAllister-Williams (2006) for a fuller review). Another source of guidance is from the British Association of Psychopharmacology (Anderson et al, 2000). These guidelines are currently being revised and are due to be published in late 2007 or early 2008 (available on the British Association of Psychopharmacology website – www.bap.org.uk). They will be a valuable addition to the NICE guidance.

Step 1: Diagnosis and recognition of depression

NICE recommends that individuals at high risk should be screened for depression. These include those who are suffering from a chronic physical illness, recently bereaved, recently unemployed and women following childbirth. Depression itself should be diagnosed with a symptom checklist to improve reliability using the *International Classification of Diseases* (10th edition) (ICD-10) criteria (World Health Organization, 1992). Severity assessment is by means of a symptom count with mild, moderate and severe defined as the presence of four, five or six, and seven plus symptoms from the checklist respectively. This guides further treatment.

Step 2: Mild depression

Antidepressants are not recommended for the routine management of patients with mild depression, but rather 'watchful waiting' which involves active follow up to identify those who remain ill. Simple advice regarding comorbid anxiety and sleep disturbance is also advised. Antidepressants are only recommended if a patient fails to respond to the above or he/she has had a history of more severe depression.

Step 3: Moderate to severe depression

The first-line intervention for moderate to severe depression is an antidepressant. An SSRI is recommended, in particular fluoxetine or citalopram. Prescribing should be done in collaboration with the patient who should be informed about what to expect from the medication. It is hoped this will improve adherence. SSRIs can occasionally cause akathisia (a subjective experience of uncontrollable motor restlessness) and increased anxiety in the early stages of treatment. This can occur with other antidepressants as well. Patients should be monitored closely since this is a risk factor for suicide. It can be managed by short-term use (2–4 weeks maximum) of benzodiazepines if simple reassurance is insufficient. If a patient fails to respond (after 4–6 weeks treatment), and lack of concordance is excluded, consideration should be given to increasing the dose of SSRIs to British National Formulary limits. If this is ineffective, there is a need to switch antidepressant. At the current time there is a paucity of data as to what factors should be taken into account when selecting between antidepressants.

Steps 4 and 5: Atypical, psychotic and treatment-resistant depression

Patients who fail to respond to two different antidepressants, or just one if they have atypical depression (characterized by 'reversed' biological symptoms of over-eating and over-sleeping), should be referred into secondary care mental health services, as should patients with psychotic depression. NICE recommends a number of possible options to manage such patients. Those with psychotic depression are recommended to receive an antipsychotic in addition to an antidepressant. Atypical depression may preferentially respond to treatment with the monoamine oxidase inhibitor phenelzine (this is not recommended for use by non-specialists). For other non-responsive patients, consideration should be given to augmenting an SSRI with lithium, using venlafaxine, combining an SSRI with mirtazepine or mianserin, or combining pharmacotherapy with an antidepressant. For severely ill, non-responsive patients, electroconvulsive therapy remains an option.

For a small but significant minority of patients there can be a less than adequate response to some or all of the treatment options recommended in the NICE guidelines.

In such circumstances referral to a tertiary level clinic specializing in affective disorders is recommended.

Conclusions

By rigorously following evidence-based guidelines, the outcome of depressed patients can be improved as has been suggested by the outcome of patients managed with treatment algorithms (Rush et al, 2006). An important additional component is the implementation of case management of depressed patients and collaborative care between primary and secondary mental health services (Gilbody et al, 2006a). While there is a clear economic argument for such services (Gilbody et al, 2006b) extra resources are needed. Research is required to gain a greater understanding of the reasons for the poor outcome and consequences of depressive illnesses. New, better tolerated and more effective treatments are also required. Better information is needed to guide treatment selection and the management of partial remission. Given the catastrophic impact of depression on both individuals and society at large, time is of the essence in this regard. BJHM

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Alonso J, Angermeyer MC, Bernert S et al (2004) Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand* **420**(Suppl): 21–7

Anderson IM, Nutt DJ, Deakin JF (2000) Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. *J Psychopharm* **14:** 3–20

Bair MJ, Robinson RL, Eckert GJ, Stang PE, Croghan TW, Kroenke K (2004) Impact of pain on depression treatment response in primary care. *Psychosom Med* **66:** 17–22

Baldwin DS, Papakostas GI (2006) Symptoms of fatigue and sleepiness in major depressive disorder. *J Clin Psychiatry* **67**(Suppl 6): 9–15

Boulenger JP (2004) Residual symptoms of depression: clinical and theoretical implications. *Eur Psychiatry* **19:** 209–13

Carney CE, Segal ZV, Edinger JD, Krystal AD (2007) A comparison of rates of residual insomnia symptoms following pharmacotherapy or cognitive-behavioral therapy for major depressive disorder. *J Clin Psychiatry* **68:** 254–60

Fawcett J, Barkin RL (1997) Efficacy issues with antidepressants. *J Clin Psychiatry* **58**(Suppl 6): 32–9

Ford DE, Kamerow DB (1989) Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA* **262:** 1479–84

Gilbody S, Bower P, Fletcher J, Richards D, Sutton AJ (2006a) Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. *Arch Intern Med* **166:** 2314–21

Gilbody S, Bower P, Whitty P (2006b) Costs and consequences of enhanced primary care for depression: systematic review of randomised economic evaluations. *Br J Psychiatry* **189:** 297–308

Goldberg D, Privett M, Ustun B, Simon G, Linden M (1998) The effects of detection and treatment on the outcome of major depression in primary care: a naturalistic study in 15 cities. *Br J Gen Pract* **48:** 1840–4

Hemingway H, Marmot M (1999) Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. *BMJ* **318:** 1460–7

Hybels CF, Steffens DC, McQuoid DR, Rama Krishnan KR (2005) Residual symptoms in older patients treated for major depression. *Int J Geriat Psychiat* **20:** 1196–202

Judd LL, Akiskal HS, Zeller PJ et al (2000) Psychosocial disability during the long-term course of unipolar major depressive disorder. *Arch Gen Psychiatry* **57:** 375–80

Keller MB, Lavori PW, Mueller TI et al (1992) Time to recovery, chronicity, and levels of psychopathology in major depression. A 5-year prospective follow-up of 431 subjects. *Arch Gen Psychiatry* **49:** 809–16

Kennedy N, Foy K (2005) The impact of residual symptoms on outcome of major depression. *Curr Psychiatry Rep* **7:** 441–6

Lingam R, Scott J (2002) Treatment non-adherence in affective disorders. *Acta Psychiatr Scand* **105:** 164–72

McAllister-Williams RH (2006) NICE guidelines for the management of depression. *Br J Hosp Med (Lond)* **67:** 60–1

Murray C, Lopez A (1996) *The Global Burden of Disease.* Harvard University Press, Harvard, CT

National Institute for Health and Clinical Excellence (2004) *Depression: Management of depression in parimary and secondary care.* NICE Clinical Guideline 23. National Institute for Health and Clinical Excellence, London

Nelson JC, Portera L, Leon AC (2005) Residual symptoms in depressed patients after treatment with fluoxetine or reboxetine. *J Clin Psychiatry* **66:** 1409–14

Ohayon MM, Schatzberg AF (2003) Using chronic pain to predict depressive morbidity in the general population. *Arch Gen Psychiatry* **60:** 39–47

Papakostas GI, Nutt DJ, Hallett LA, Tucker VL, Krishen A, Fava M (2006) Resolution of sleepiness and fatigue in major depressive disorder: A comparison of bupropion and the selective serotonin reuptake inhibitors. *Biol Psychiatry* **60:** 1350–5

Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A (1995) Residual symptoms after partial remission: an important outcome in depression. *Psychol Med* **25:** 1171–80

Paykel ES, Scott J, Teasdale JD et al (1999) Prevention of relapse in residual depression by cognitive therapy: a controlled trial. *Arch Gen Psychiatry* **56:** 829–35

Pratt LA, Ford DE, Crum RM, Armenian HK, Gallo JJ, Eaton WW (1996) Depression, psychotropic medication, and risk of myocardial infarction. Prospective data from the Baltimore ECA follow-up. *Circulation* **94:** 3123–9

Rush AJ, Trivedi MH, Wisniewski SR et al (2006) Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* **163:** 1905–17

Thase ME (1999) Antidepressant treatment of the depressed patient with insomnia. *J Clin Psychiatry* **60**(Suppl 17): 28–31

Thomas CM, Morris S (2003) Cost of depression among adults in England in 2000. *Br J Psychiatry* **183:** 514–19

Tranter R, O'Donovan C, Chandarana P, Kennedy S (2002) Prevalence and outcome of partial remission in depression. *J Psychiatry Neurosci* **27:** 241–7

Trivedi MH, Rush AJ, Wisniewski SR et al (2006) Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry* **163:** 28–40

World Health Organization (1992) *The ICD-10 Classification of Mental and Behavioural Disorders.* World Health Organization, Geneva

KEY POINTS

- Depression is associated with high levels of morbidity and mortality.
- Depression is treatable although many patients do not reach full remission of symptoms with first-line treatments.
- Partial remission, with residual depressive symptoms, is a therapeutic target in its own right since this state is associated with poor social functioning and high rates of relapse to a full-blown episode of depression.
- Stepped care management of depression following National Institute for Health and Clinical Excellence guidelines is recommended.