Feeling unhappy about being ill seems so understandable – but it is easy to forget that the majority of people do not suffer from sustained low mood when they have a physical disease, even a chronic and disabling one (see Robertson and Katona 1997, for review). For those who do have a depressive disorder co-existent with physical illness, the result seems to be a lower quality of life, and worse outcomes from treatment (Creed et al. 2002). The recognition and treatment of co-existent depression ought therefore to be a part of the management of all chronic disease, and neurology is no exception.

Review articles, like chess games, have a limited number of conventional openings. The next move in developing the current argument would normally be to lament the hopelessness of most doctors when it comes to recognizing depression in their clinical practice, before going on to offer the Psychiatrists' Gambit – routine use of a screening instrument followed by treatment, or referral for high scorers. Variations revolve around the specifics of the recommended screening instrument and antidepressant medication. This line is familiar and looks plausible, but it has a flaw and that is – we don’t know exactly what we mean by depression. If we don’t know what we’re looking for then it’s not surprising that depression is under-recognized or that advice about best treatment is so hard to come by.

DEFINING DEPRESSION AND DEPRESSIVE DISORDERS

Emotional disorders such as depression are named by the predominant mood state with which they are usually associated, but emotional changes other than just unhappiness are also recognized as depressive. In particular, a loss of feeling (apathy) and a loss of sense of pleasure (anhedonia) fit the idea of lowered mood inherent in the use of the word depression. Although emotions such as anxiety and irritability may be relatively discrete, they can also often appear as part of the undifferentiated or non-specific mood change that accompanies any state of distress – think of grief. So the most obvious prevailing mood disturbance in depression may not be depression!

Furthermore there are other components to those mental states usually labelled as emotional disorders. Characteristic styles of thinking accompany mood change, as do certain sorts of behaviour – the latter sometimes driven by particular thoughts and sometimes not. For example, social withdrawal may arise as a response to thoughts about personal worthlessness or it may be a symptom of the physical inertia and lack of drive that can accompany depression. Certain physical symptoms such as sleep disturbance and loss of appetite are typical of emotional disturbance although not of course unique to it.

The main emotional (ie affective), behavioural, cognitive and somatic components of emotional disorder are shown in Table 1.

Faced with the range of symptoms that might be called depressive, then how might depressive disorder be defined? One reasonable summary of current clinical usage would be to define depression as ‘any negative or unpleasant emotion that is not purely anxiety, irritability or anger, and that is associated with a greater or lesser amount of cognitive behavioural or physical change.’ Taking this broad approach to defining the emotional component of depression, what makes for a depressive disorder? That is, when should depressive symptoms be considered abnormal? There are three main approaches discernible in practice.
Diseases crucify the soul of man, attenuate our bodies, dry them, wither them, shrivel them up like old apples, make them so many anatomies.

Robert Burton,
The Anatomy of Melancholy 1621
The setting of a threshold to define disorder is problematic; there is no clear level below which depressive symptoms have no impact on outcomes, although relatively little research has been done in this area, and there is no biological criterion (gold standard) to which one can appeal. The upshot is that cut-offs used to define disorder either have a rather arbitrary feel to them, or they are derived by appeal to a diagnosis based on psychiatric interview, standardized or not.

Which takes us to the second method for defining depressive disorder – the presence of a more-or-less specific depressive syndrome identified at interview. These syndromes are derived from the symptoms shown in Table 1, but some symptoms are regarded as more important than others. The best known is the major depressive syndrome now included in the two main psychiatric diagnostic systems: the World Health Organisation’s ICD-10 (1992) and the American Psychiatric Association’s DSM-IV (1994) (Table 2).

The third approach is more recent, and related somewhat to the syndromal approach to defining depressive disorder – the presence of a more-or-less specific depressive syndrome identified at interview. These syndromes are derived from the symptoms shown in Table 1, but some symptoms are regarded as more important than others. The best known is the major depressive syndrome now included in the two main psychiatric diagnostic systems: the World Health Organisation’s ICD-10 (1992) and the American Psychiatric Association’s DSM-IV (1994) (Table 2).

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The third approach is more recent, and related somewhat to the syndromal approach to defining depressive disorder. However, the emphasis is on certain key symptoms, particularly in the cognitive domain. Ideas of hopelessness or helplessness, or a sense of low self-esteem or lack of self-worth, are seen as key components of depressive disorder. It has been argued (although the idea has not really caught on) that the depressive syndromes should be defined in the presence of severe physical illness to include more of these cognitive items and to exclude physical symptoms of emotional disorder (Endicott 1984).
Conclusion: which approach to the definition of depression?

Each of these three approaches has its advantages. Symptom burden is a major determinant, and perhaps the defining characteristic of quality of life. An over-emphasis on syndromal approaches downplays the undifferentiated nature of much distress. Depression symptom levels below those necessary to meet diagnostic criteria, so-called sub-syndromal depression, nonetheless do affect outcomes. On the other hand, not all emotional disorder is undifferentiated distress and the ability to identify specific syndromes can have an important part to play in deciding treatment. The main diagnostic systems take account of duration of symptoms in defining disorder, unlike measures of current symptom burden. Specific mood-related cognitions have come to be recognized as important determinants of outcome of depressive episodes, and perhaps also of physical morbidity. These cognitions, and behaviours associated with them, form the focus for brief psychological therapies such as cognitive-behaviour therapy and problem-solving therapy.

In summary, there are three overlapping ways of defining depressive disorder:

- high levels of symptoms that are not attributable to the direct consequences of physical disease, and that are recognizably those of emotional disorder;
- the presence of a depressive syndrome as defined by one of the standard diagnostic symptoms;
- the presence of depressive symptoms not in themselves sufficient to make a psychiatric diagnosis, but associated with specific negative cognitions that are typically associated with emotional disorder.

This inclusive approach to definition is likely to be more useful to the neurologist than one based on applying a single set of criteria, which too often leads to the neglect of important emotional disorder because the hapless patient does not match the definition of ‘real’ depression (also known as clinical depression or depressive illness).

RECOGNIZING DEPRESSIVE DISORDERS

Regardless of the definition chosen, there are reasons why depressive disorders might be easy to miss in neurological practice, even more so than in any other busy clinical environment. Neurological disorders can cause difficulties with emotional expression so there is a disjunction between felt emotion and emotional behaviour; the rhythm and intonation of speech may be disturbed (aprosody) so that emotion is not conveyed normally; facial and bodily movement may be reduced or abnormal. There is an additional diagnostic difficulty if the patient has a language deficit or cognitive impairment.

It is for these reasons that an active approach to case-finding is so often advocated, aided by the use of standardised methods for the identification and measurement of depression.

Self-report mood measures are well-established and Table 3 shows some of the more widely used scales. They are (as noted earlier) measures of symptom burden. One problem with their use in the neurological context is relatively high non-completion rates – typically in the order of 20–25% – that arise mainly because of physical incapacity and cognitive impairment. Even in those who can complete them, there are difficulties in interpreting the results, notably because most include symptoms that could be attributed to the direct effects of physical disease rather than to any co-existent mood disorder. The effect is two-fold. Firstly, self-rating scales tend to be sensitive but not very specific when it comes to identifying depressive syndromes such as major depression (Bjelland et al. 2002). Secondly, the best cut-off to use for identification of a depressive syndrome will vary according to both the nature of the neurological disorder itself, and to the stage of disease and its treatment (Bridges and Goldberg 1986).

A well-known response has been the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith 1983), in the construction of which items that referred to physical symp-
toms were replaced with other more cognitive or emotional items. On the face of it this should have led to a more specific mood measure but there are doubts, with more than one study showing similar specificities to the other measures (O’Rourke et al. 1998, Bjelland et al. 2002). In any event, the logic of the situation is a little unclear when the validation criterion in most studies has been the presence of the major depressive syndrome, which itself includes a number of somatic items.

With sensitivities of about 75–80%, and specificities of about 65–75%, mood rating scales will have a positive predictive value of 20–30% if they are used in a clinical population where the prevalence of depression is somewhere in the range of 10–20%. This imprecision – coupled with doubts about what is being identified and why – accounts for the rarity with which self-report measures are used in routine neurology practice. Especially in a busy outpatients clinic, the effort does not seem worth the potential reward. Indeed, routine use of mood rating scales in non-psychiatric settings has not been shown to improve patient outcomes, so perhaps this clinical intuition is right (Gilbody et al. 2001).

**Interview-based assessment** is more accurate and can be applied to almost everybody. The most important questions can be asked by any clinician with basic interviewing skills and this does not require any special psychiatric training. The main items for inquiry are given in the Box (opposite). It may be that such an interview will be more effective if preceded by administration of a self-report mood measure – if that measure is scored beforehand and the result is available so the interviewer knows if the patient has a high score. In this context a high score should not lead to a clinical management decision but it acts as a decision aid, by changing one’s prior probabilities of the diagnosis of depression.

**Non-language-based assessment** of mood is needed for patients who have communication or cognitive problems that prevent use of one of the standard questionnaire or interview methods. There are three options: visual analogue scales, Likert-type scales based on images like smiley faces, and observation-based measures. The first two approaches have not been evaluated formally but my own experience is that people who don’t have enough language to participate in a standard assessment can’t complete these alternatives. Observational methods have been evaluated, with mixed results (Sutcliffe and Lincoln 1998, Hammond et al. 2000). Nonetheless they do better than chance – adding some precision to an informed clinician’s observations and intuition.

### Table 3: Widely-used self-report scales of mood disturbance

<table>
<thead>
<tr>
<th>SCALE</th>
<th>NUMBER OF ITEMS</th>
<th>CONTENT</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck Depression Inventory&lt;br&gt;<em>Beck et al. (1988)</em></td>
<td>21</td>
<td>Depression&lt;br&gt;Affective, cognitive and somatic items</td>
<td>Widely used in general population and medical patients</td>
</tr>
<tr>
<td>General Health Questionnaire&lt;br&gt;(GHQ 28; <em>Goldberg and Hillier (1979)</em></td>
<td>28</td>
<td>Depression&lt;br&gt;Anxiety&lt;br&gt;Social dysfunction</td>
<td>Widely used in general population and somatic medical patients</td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale&lt;br&gt;<em>Zigmond &amp; Snaith (1983)</em></td>
<td>14</td>
<td>Anxiety&lt;br&gt;Anhedonia</td>
<td>Excludes biological symptoms and most cognitive symptoms of depression</td>
</tr>
<tr>
<td>Wimbledon Self-Report Scale&lt;br&gt;<em>Coughlan &amp; Storey (1988)</em></td>
<td>30</td>
<td>Depression&lt;br&gt;Irritability&lt;br&gt;Anxiety</td>
<td>Excludes somatic items</td>
</tr>
<tr>
<td>Wakefield Depression Inventory&lt;br&gt;<em>Snaith et al. (1971)</em></td>
<td>12</td>
<td>Depression</td>
<td>Designed to assess severity of depressive illness</td>
</tr>
<tr>
<td>Zung Self-Rating Depression Scale&lt;br&gt;<em>Zung (1965)</em></td>
<td>20</td>
<td>Depression</td>
<td>Designed to assess severity of depressive illness</td>
</tr>
<tr>
<td>CES-D&lt;br&gt;<em>Roberts &amp; Vernon (1983)</em></td>
<td>21</td>
<td>Depression</td>
<td>Widely used in USA, especially in epidemiological surveys in the community</td>
</tr>
</tbody>
</table>
Conclusion: when and how to look for depressive disorders

It isn’t easy to set rules for a programme of assessment for depression in the management of neurological disorder. Depression can appear at any time, not least because it may arise in response to events quite outside the neurological disorder, while nonetheless having an important relation to the outcome of that disorder. However, because depression is very often a response to recent stressful events (Brown and Harris 1987), there is a case for looking for it at certain times in the course of an illness, or if you like at certain points on the care pathway:

- in the first three months or so after diagnosis;
- at the time of hospital admission, perhaps most usefully prior to discharge;
- during active rehabilitation, especially early on when untreated depression may influence outcomes;
- during follow-up for chronic disease, especially after any deterioration or new event.

Particularly at risk are those with a history of a previous depressive episode and those with poor social support as a result of either absent or unsupportive key relationships.

A brief clinical interview can cover the main items, preferably (but not essentially) preceded by administration of a self-report mood scale. Which one probably isn’t that important. What matters is that it has already been scored when the interview is conducted and you have some familiarity with the scoring system and the likely meaning of a particular score. For specific conditions, a key nurse or specialist nurse is ideal but this interview can be conducted by any member of the clinical team with a bit of time. It need not take more than 10 minutes; that’s all the time general practitioners spend on most consultations and they deal with 90% of all depression seen in clinical practice.

MANAGING DEPRESSIVE DISORDERS

Of course there’s not much point in identifying depression if you don’t know what to do next. For the neurologist there are four main options: wait and see, optimise general clinical care, try antidepressant medication, and refer to a mental health professional.

Wait and see

Much depression is transient, particularly when it arises in response to an immediate stressor when it can be thought of as rather like grief. The best course of action may therefore be to wait and see if it resolves spontaneously. It is worth waiting at least 2 weeks and probably about a month before repeating an assessment but not much longer. Perhaps surprisingly, mood disorder that hasn’t resolved within 4–6 weeks after even major stress is likely to persist for months without intervention. A follow-up assessment may therefore have to be arranged by a specialist nurse, or with the general practitioner. This does however require active management: just who exactly is going to check again? You could ask the patient to go back to see somebody, but depression reduces motivation to act on that sort of advice.

There are two circumstances in which a wait-and-see policy isn’t justified. One is when you know already that the depression is persistent; most people can date the onset of a depressive disorder reasonably accurately. The second is when symptoms require a rapid response regardless of their duration. Most pressingly this means suicidal thinking, but it can include other dangerous features such as poor fluid or dietary intake, or extreme withdrawal and immobility.

INDICATORS OF POSSIBLE DEPRESSIVE DISORDER

- Symptoms of emotional disturbance (Table 1)
- Multiple or unexplained physical symptoms
- Thoughts that life is not worth living
- Undue hopelessness
- Suicidal thoughts
- Helplessness
- Undue dependence on others
- Poor adherence to treatment
- Excessive handicap in relation to impairment and disability
Optimising general clinical care

Depressive symptoms are positively associated with disability levels, which makes sense in one way; the greater the stressor (physical disorder), the stronger the response to it (depressive disorder). In addition, there is some evidence that people with depressive disorders get less active treatment for physical illness (Druss et al. 2001), and that they compound the problem by adhering less well to treatment (DIMatteo et al. 2000), so there may be secondary explanations for the association between depression and disability.

Whatever the explanation, it would seem plausible that assertive treatment of physical illness and its associated disability would lead to improvement in mood symptoms. Rather surprisingly, the evidence for this is not strong. The reason is probably that depression arises in response to the meaning given to an illness by the patient as much as it does to the physical impact of the illness, and the meaning to the patient may not be readily changed by the experience and effects of physical treatment. This constellation of chronic illness that is not being treated very actively (for whatever reason), poor adherence to any treatment that is offered, and negative interpretation of the illness experience can all help to sustain depression.

An important element of the meaning of illness, and therefore of the response the patient makes to it, is the degree to which the patient feels in control of the illness or able to affect its treatment or outcomes (see Petrie and Weinman 1997 for a review). For that reason the role of supportive input from specialist nurses or other staff (such as stroke family support workers) might be beneficial if the result is to increase the resources available to the patient. The elements of effective support are emotional (includes confiding, sharing) and practical or instrumental (includes information, practical help). On the other hand, extra 'support' may be of no value (or positively harmful) if all it does is engender in the patient a sense of dependence on professional help. This dilemma may account for the contradictory results obtained from research into the benefits of providing additional support to people living with chronic illness (Dennis et al. 1997, Mant et al. 2000), because studies that included reasonable numbers of patients were assessing the impact of very few (perhaps only one) support worker.

This supportive role is usually taken on by specialist nurses or social workers. The evidence is not good (Knapp et al. 2000), but it is reasonable to assume that they are more likely to be effective in alleviating depression if they have had some training in brief psychologically-oriented interventions such as communication skills, motivational interviewing and problem-solving therapy. Such a service should probably be offered to all patients who are suffering from depression associated with chronic neurological disorder.

Rational use of antidepressants

Antidepressant therapy should be offered to anybody with a persistent depressive disorder who has not responded to efforts at optimising physical care and providing professional help for coping with illness (Gill and Hatcher 2003).

For practical purposes, the non-specialist can think of antidepressants as falling into three classes:

- tricyclic and related antidepressants;
- specific serotonin reuptake inhibitors (SSRIs);
- monoamine oxidase inhibitors (MAOIs) – best kept for specialist use.

You should therefore familiarise yourself with one or two members of each of the first two classes. My own preferences are for dothiepin or lofepramine from the former group, and fluoxetine from the latter. The general principle is to undertake a therapeutic trial of a drug from one class, switching to a trial of a drug from the other class if there is no benefit after 6–8 weeks of the first drug. I start with a tricyclic or related drug if there might be some benefit from a degree of sedation (insomnia, anxiety) or if there are physical symptoms that might benefit simultaneously (such as chronic pain, bladder instability). SSRIs have less effect on epilepsy threshold.

A therapeutic trial involves starting with a moderate daily dose of a suitable antidepressant – for example 75 mg dothiepin, 140 mg lofepramine or 20 mg fluoxetine (Furukawa et al. 2002). If there is no response in 2–3 weeks, then increase the dose (e.g. 150 mg dothiepin, 210–280 mg lofepramine, 40 mg fluoxetine). There is no point in going higher, this will produce more adverse effects but no extra benefit for most people (Bollini et al. 1999). A common mistake is not to evaluate the effect of this therapeutic trial and take effective follow up action. If the trial is successful then the antidepressant should be continued for 6 months, after which it can be tailed off over 4–6 weeks to minimise the likelihood of withdrawal symptoms that occur in a minority of cases. If the trial is unsuccessful
then the drug should be stopped. Failure of two antidepressant drugs is a reasonable criterion for referral to a mental health professional. The main other option is simply to wait and see if the patient is sunken on referral. There is unlikely to be benefit from further trials of antidepressants without assessment by a specialist.

Referral and the role of brief psychological therapies
You should consider specialist assessment when the handicap of a proportion to impairment and disability, or when there are unexplained symptoms (including physical symptoms) that might be compatible with emotional disorder. Also, refer for advice about treatment when an identified depressive disorder has not responded to the first line treatments outlined above.

The modern drug treatment for persistent or resistant depression starts with ensuring that there has been a good trial of the basic drugs. It usually then involves combination therapy with an antidepressant and an adjuvant such as lithium, not because the evidence is good (Stimpson et al. 2002) but because without therapy the outcomes are poor. These multi-drug regimes are not without adverse effects and treatment should be planned in collaboration between the neurologist and psychiatrist.

One of the major developments in mental health practice in recent years has been the emergence of a number of brief psychological therapies, most popularly cognitive-behavioural therapy but also therapies that focus more on relationships, so-called interpersonal therapies (Elkin et al. 1992) or on dilemmas of daily living (problem-solving or problem-oriented therapies). They have the advantage that they are feasible for use in routine National Health Service practice and are acceptable to patients, and they are the main alternative to drug treatment in specialist care. Some of these interventions, especially the more behaviourally-oriented, are suitable for people who would traditionally have been thought of as unsuitable for psychotherapy – such as those with schizophrenia or traumatic brain injury – so that some degree of cognitive impairment due to neurological disorder is not an absolute contra-indication.

Finally, although there is not supportive research evidence, most of us think that this is specialist work. Neurologists should find colleagues with an interest in liaison psychiatry and clinical health psychology (not just neuropsychology) to help with these challenging problems.

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