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Depression is the commonest psychiatric disorder in the industrialised world. Many patients are now diagnosed and treated with effective antidepressants by primary care physicians. A large proportion of depressed individuals fail to reach their premorbid level of functioning following a course of treatment; estimates vary from 10% to 30% (Nierenberg & Amsterdam, 1990). These individuals require a major input from the services and suffer prolonged distress, with many adverse personal, social and economic consequences.

Kraepelin's division of functional psychosis on the basis of the course of the illness led to the characterisation of depression as a self-remitting disorder. Before the introduction of effective antidepressant treatments, episodes of depression usually lasted 9–12 months (Kraepelin, 1913). Depression that did not respond to the available management strategies was considered a 'character neurosis' or 'depressive personality'. The introduction of tricyclic antidepressants added to the optimistic view of depression as an episodic and treatable disorder. In the last few decades, increasing evidence has accumulated that depression can, and often does, become treatment resistant and chronic, with consequent high morbidity and mortality (Keller *et al*, 1984; Lee & Murray, 1988).

Definition

The term 'treatment resistant depression' pressumes that there is an agreed and widely shared range or combination of treatments that are used in a standardised way for treating depression. In practice, treatment strategies vary widely. General practitioners prefer to use low, sometimes inadequate doses of older drugs, or the newer, less toxic compounds. In the absence of research-based guidelines, psychiatrists devise treatment plans based upon personal experience and anecdotal evidence, with differing emphasis upon other treatment options such as psychotherapy. Research definitions for resistant depression also vary widely (Nierenberg & Amsterdam, 1990).

One simple and clinically useful definition of resistant depression is a failure of response to an adequate trial of antidepressant treatment (Nelson & Dunner, 1993). In 1974, the World Psychiatric Association proposed that treatment resistance should be divided into absolute resistance and relative resistance. Absolute resistance was defined as a failure of one adequate antidepressant trial specified as four weeks of 150 mg/day of imipramine or its equivalent. A poor response to an inadequate course of treatment was called relative resistance. This distinction emphasises the need for an adequate trial of antidepressants before a patient is considered treatment resistant.

Causes

The lack of consensus on the definition, phenomenology, and the causation of resistant depression has made it largely "a labelling phenomenon... Patients have refractory depression because they have been labelled as such" (Guscott & Grof, 1991). The label

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may have been applied to a wrong diagnosis, to an inadequately treated episode, to a poorly compliant individual, or without consideration for events perpetuating the depression.

Diagnostic considerations

Keller *et al* (1986) found that a long index episode of depression predicted a worse outcome in subsequent episodes. A delay in initiating active treatment is an important predictor of the length of the illness episode (Scott & Eccleston, 1991), and may therefore be related to subsequent resistance. Depression may also be overdiagnosed. In one study, 13.3% of cases of resistant depression had a primary disorder other than affective illness (MacEwan & Remick, 1988). Physicians give precedence to a diagnosis for which treatment is available and the prognosis is good. This, and a changing therapeutic expectation, have shifted diagnostic practice towards affective disorders (Whybrow *et al*, 1984). Hence it is important to confirm the diagnosis by reviewing all available information before any individual is considered treatment resistant.

Inadequate treatment

By definition, treatment resistance depends upon the notion of adequate treatment. Over the years, the recommendation of adequate dosage has increased from 150 mg/day to 250–300 mg/day of imipramine or its equivalent (Nierenberg, 1992); and duration of trial from 3 to 6 weeks (Quitkin, 1984). Plasma level monitoring of the drug can be used to assess the adequacy of dosage if suboptimal dosing is suspected.

Compliance

Compliance with antidepressant medication is a complex and multifaceted problem (Book, 1987). Many people still believe that psychotropic drugs are addictive. Others hold the attitude that taking pills for emotional problems avoids tackling the underlying psychosocial 'causes' of depression. Medication is seen either as 'an emotional crutch' (Guscott & Grof, 1991) or as a means of numbing feelings that should be expressed appropriately in some form of psychotherapy. Patients find the anticholinergic side effects of first-generation antidepressants quite unpleasant, especially if these have not been discussed before commencement of therapy. Therapy is often terminated prematurely by patients following a remission in symptomatology. Any of these factors may be responsible for poor compliance and an inadequate recovery from depression which is then considered resistant. Compliance can be assessed both by plasma level monitoring and by a detailed, non-judgmental exploration of the worries, attitudes and beliefs of patients and their families about medication.

Treatment paradigm used

A rational, carefully considered, step-by-step approach through different options is necessary before a patient is considered treatment resistant. Several treatment paradigms have been proposed for managing resistant depression. These involve using two different tricyclic antidepressants at full doses as the first and second step; trying a serotonin-specific reuptake inhibitor (SSRI); adding lithium or antipsychotics to the tricyclic agent; and using a monoamine oxidase inhibitor (MAOI) drug. Various augmentation and combination strategies of antidepressants with triiodothyronine (Joffe & Singer, 1992), psychostimulants (Warneke, 1990), tryptophan (Young, 1991) and anticonvulsants such as carbamazepine (Post *et al*, 1986) and valproate have also been tried. Electroconvulsive therapy (ECT) can be especially useful in some resistant patients (Avery & Lubrano, 1979). Sleep deprivation (Dessauer *et al*, 1985), bright light therapy (Levitt *et al*, 1991) and psychosurgery (Bridges, 1991) have also been recommended in resistant depression. There is a dearth of experimental data to show the efficacy of one particular strategy over the other, and this remains a major challenge for the future.

Depressive subtypes

Depression is a heterogeneous group with many subtypes, requiring different treatment approaches. Clinically important ones include the following.

Delusional/psychotic depression Delusions and other psychotic phenomena occur in 20–30% of depressed patients. Such patients may fail to respond to antidepressants alone and the addition of antipsychotic medication or ECT is necesary to produce remission.

Double depression This is an episode of acute major depression superimposed on a chronic

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depression or dysthymia (Keller & Shapiro, 1982). These patients have more severe depressive symptoms, greater comorbidity, more personality disturbance, lower levels of social support, more psychosocial stresses, greater familial loading, greater impairment and a relatively worse outcome than patients with episodic depression (Klein *et al*, 1988).

Atypical depression This refers to depression with high anxiety, abnormal fatigue and reverse vegetative shift in the presence of mood reactivity. Klein & Davis (1986) named it hysteroid dysphoria, to emphasise the patient's extreme sensitivity to rejection in interpersonal relationships. These patients respond better to MAOI drugs as compared to tricyclic antidepressants (Stewart *et al*, 1993).

Rapid cycling affective disorders Rapid cycling, defined as the occurrence of four or more affective episodes in a year (Dunner & Fieve, 1974), may show resistance to antidepressant therapy. Rapid cycling has been reported to be more common in patients attending lithium clinics (Wehr & Goodwin, 1979). Subclinical hypothyroidism has been implicated in rapid cycling (Cowdry *et al*, 1982). Various combinations of lithium with tricyclic antidepressants, thyroxine, carbamazepine and clorgyline have been recommended for treating this condition (Alarcon, 1985).

Comorbidity

With physical illness Depression can occur as a presenting complaint in many physical disorders. The commonest of these is hypothyroidism. Thyroid augmentation of antidepressants is a useful strategy in managing treatment resistance even in the absence of clinical or biochemical hypothyroidism (Nelson & Dunner, 1993). Other endocrine disorders, certain malignancies, drugs, vitamin deficiencies, electrolyte imbalance and viral infections must also be considered in cases of resistant depression. Recently it has been reported that depression following a minor head injury, though syndromally indistinguishable from a functional depression, is resistant to tricyclic antidepressants (Dinan & Mobayed, 1992).

With psychiatric disorders Depression often presents with other disorders, especially anxiety, panic and personality disorders. Although research in these areas is still controversial, the comorbidity of depression with axis II disorders or anxiety disorders has been associated with chronicity and treatment resistance (Nelson & Dunner, 1993).

Ongoing psychosocial stresses

Adverse life events often precipitate an episode of depression. Depressive illness, by impairing coping abilities, makes individuals more susceptible to adverse events. Thus a series of adverse life events accumulate, making the original depression worse. Although such a formulation intuitively makes sense and is seen in clinical practice, research in this area has not produced unequivocal results. Scott & Eccleston (1991) found that multiple life events before and after the onset of illness episode predisopose an individual to develop a chronic course. Hirschfeld *et al* (1986) did not find any differences in life events, early losses, and social support, when recovered depressives were compared with those who had not responded to treatment. This is clearly an area that requires further research.

Treatment resistance in the elderly

Depression poses many special problems in the elderly population. It differs in clinical presentation, with somatisation and pseudodementia; can be secondary to an underlying physical illness or medication; and may be dismissed as an inevitable accompaniment of ageing, thus delaying effective treatment. Adverse life events, especially bereavement, and major physical illness occur more frequently in this group. The elderly are also more susceptible to the side effects of antidepressants. Resistant depression is particularly common in this population, and about 15% are chronically, unremittingly depressed. This chronic state, called 'residual depressive invalidism', shows persistent cognitive and emotional changes of depression and predisposes the individual to further, recurrent episodes of major depression (Murphy & Macdonald, 1992). This puts an enormous burden on the carers and is particularly distressing for the sufferers. Elderly patients are likely to receive inadequate doses of medication for brief periods, and hence be labelled as treatment resistant more often.

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Consequences of resistant depression

Quality of life

Depression, by affecting all aspects of life, has a profound impact upon the quality of life. Styron (1991) has given a vivid first-person account of the devastating effect of depression on his life, and called it a 'despair beyond despair'. Anhedonia is particularly distressing, as patients struggle to come to terms with an inability to experience pleasure from loved ones, work or leisure activities. Poor performance and long periods of absence from work can result in unemployment with considerable personal and financial adversity. Mintz *et al* (1992) found that work recovery in depression is slower than symptomatic recovery, with very poor occupational outcome in those with a high relapse rate. In refractory depression such adversities can become the ongoing stressors that perpetuate a cycle of mounting hardships and worsening coping abilities.

Enduring personality changes

Long standing depression can produce non-affective changes in personality. Premorbid personality traits may become exaggerated. Neurotic traits, chronic anxiety, passive dependence, hostile egocentricity and obsessionality may emerge (Cassano *et al*, 1983). Prolonged depression can produce a blunting of mood reactivity and a loss of emotional resonance. Enduring cognitive changes with demoralisation, apathy and hopelessness may alter the individual's way of perceiving and relating to the self and the outside world. ICD–10 (World Health Organization, 1992) has a separate category, F62.1, for personality changes following a major mental illness. This recognition was long overdue.

Morbidity and mortality

Prolonged depressive illness makes people vulnerable to many physical disorders. Self neglect, poor nutritional intake and weight loss in particular make individuals who may not seek help for physical problems in time susceptible to illness. Depressed individuals may turn to alcohol either through despair or as their only means of emotional solace and physical relaxation. This further contributes to the physical decline. There is a higher mortality among depressed people as compared to the normal population, both due to natural causes like cancer and cardiovascular diseases, and unnatural causes, especially suicide (Lee & Murray, 1988).

There is a strong relationship between suicide and depression. Depression is the commonest preceding disorder in complete suicides. Depressives who commit suicide, when compared with a control group, have more persistent insomnia, more self-neglect, more memory impairment, are more agitated, more socially isolated and have made more suicide attempts (Barraclough & Pallis, 1975).

Effect on relatives

Psychiatry has justifiably been criticised for emphasising the role of family in the genesis of mental disorders while ignoring the consequences of such disorders on family members. Depression can place an enormous burden upon the family and carers. The demotivation, anhedonia, social withdrawal, prolonged sleep disturbance, erratic eating pattern, retardation and negative ruminations that so characterise depression can put the emotional fabric of even the most close knit and loving family under strain. Family members can suffer from various neurotic and stress-related disorders as a result of looking after a depressed individual. This stress is likely to worsen as the duration of depression increases. The cycle of raised expectations at the initiation of a new therapy that does not bear fruit can steadily worsen this stress as the patient and family members lose hope. Immense feelings of guilt, hostility, ambivalence and self-criticism may be generated in the family members. The emotional, social and economic burden of this prolonged distress can only be imagined, since no reliable way of quantifying these is available.

Effect on clinicians

Patients who do not respond to treatment can generate negative feelings in their treating clinicians. These vary from a sense of frustration, incompetence, and ineffectuality to unconscious anger and resentment at the continuing expression of distress by the patient (Guscott & Grof, 1991). The change of diagnosis from depression to personality disorder at this stage is an unstudied, and possibly unacknowledged phenomenon.

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Financial costs

These result from the direct costs of the illness like hospitalisation, medication and other medical costs; and indirect costs that result from time lost from productive work. It has been estimated that the financial costs of depression in the USA amount to approximately $16.3 billion per year (Stoudmire *et al*, 1986). It is likely that a high proportion of this enormous financial burden results from resistant depression.

Future directions

There are several ways to develop better strategies for managing treatment resistance in depression. Adequate treatment of the initial episode and suitable prophylaxis against relapse can prevent the condition becoming established. Prolonged treatment with full dose antidepressants has recently been shown to be the best available prophylactic strategy (Kupfer *et al*, 1992). Lee & Murray (1988) found that a high proportion of chronically depressed were not in current contact with psychiatric services. The ongoing Defeat Depression campaign, and other public education programmes can play a very useful role by challenging the continuing stigma of mental illness and the associated discrimination against the mentally ill. A high public profile of these issues can help change attitudes towards treatment and encourage patients to re-establish contact with the services. Many unanswered questions in this area demand further research. What clinical variables predict treatment resistance? What biological markers distinguish this group from treatment responders? Are there differences in treatment resistance among unipolar and bipolar depressives? Are there any clinical subtypes of resistant depression? The answers to these, and a better understanding and treatment of resistant depression are a fitting challenge for psychiatry in the twenty-first century.

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