CHAPTER 1

Diagnosis of Depressive Disorders

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INTRODUCTION

> *Taxonomy is described sometimes as a science and sometimes as an art, but really it's a battleground.*
>
> —Bill Bryson (2003)

Any diagnostic system depends on a classificatory model. Prior to the introduction of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III) model for classifying depressive disorders in 1980 there was controversy over how depression should be classified. This controversy was largely to do with contrasting unitary and binary models of depression. The DSM-III resolved the debate in favour of a primarily dimensional model (a unitary approach). This model was also adopted in the World Health Organization's *International Classification of Diseases*, 10th Revision (ICD-10) (1992), which emerged in the following decade. As with any clinical domain that is modelled dimensionally, there are problems in defining when a particular individual's presentation should be considered a clinical 'case' and in readily identifying any differences in the usefulness of particular treatments for particular presentations.

This chapter provides an overview and critique of the current DSM and ICD systems of classification and highlights limitations that arise from their dimensional approach and lack of theoretical basis regarding cause. An alternative model by McHugh based on aetiopathic clusters is also discussed and a mixed categorical and dimensional model developed by the author and others is presented. The mixed model proposes that depression exists at multiple levels – normal, syndrome and disease – and seeks to define the clinical depressive disorders using phenomenological and aetiological distinctions (i.e. distinctions related to the person's experience of the disorder and/or its cause).

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What is 'depression'?

'Depression' is, at first pass, a broad nonspecific term, encompassing multiple normal mood states as well as disorder and disease states.

A *depressed affect* is a state of feeling 'depressed', 'sad' or 'blue', usually in response to a specific trigger, that generally resolves within minutes to days – either due to reprieve from the stressor or the individual experiencing a spontaneous restoration of mood.

A *depressed mood* is more pervasive. It is more likely to be experienced by the individual as a drop in their sense of self-worth and self-esteem and is associated with depressive ruminations, such as feeling hopeless and pessimistic. It may or may not affect functioning. Experienced by most people, and again usually occurring in response to a negative stressor (particularly a loss that impacts on the individual's self-esteem), it may last minutes to days before resolving spontaneously or in response to neutralising of the stressor.

Three features – depressed mood, lowered self-esteem and increased self-criticism – distinguish depression phenomenologically from *grief* and *bereavement,* where, despite a distinct sense of loss of something valued, there is no primary loss of self-esteem. The mood features of depression also assist phenomenological distinction from *anxiety*, where a sense of fear, apprehension, worry, panic or of 'going mad' is more likely to be reported.

Episodes of depressed mood are experienced by most people, and may be described as 'blue' states or even 'normal' depression. By contrast, current definitions of *clinical depressive conditions* generally (i) have their 'caseness' status defined by severity (i.e. they are more severe, persistent and/or recurrent), (ii) have symptoms that are more pathological in status and (iii) are impairing or disabling.

Classifying depression – What do we want and why do we want it?

It might be useful to consider what we should expect of a classificatory system of the depressive disorders before considering what is available.

Firstly, we would almost certainly require it to define 'clinical' depressive states and distinguish them from 'normal' depressive mood states. Secondly, we would wish to have decision rules that differentiate unipolar from bipolar expressions of clinical depression (i.e. differentiating longitudinal patterns of depression only from oscillating depressive and 'high' episodes). Thirdly, we might want it to quantify severity, duration, recurrence or other dimensional parameters. This third classificatory option is less important, however, as these more define illness course than illness type.

Fourthly, above and beyond these minimal requirements, we might expect the system to divide the broad category of clinical depression into those subtypes that have differential clinical patterns, causes and/or intrinsic responses to different treatment modalities. The two key candidate depressive conditions for such subtyping are psychotic depression and melancholic depression. Assuming that these are categorical subtypes, we would expect clear clinical definition (principally embracing clinical symptoms and signs) that would differentiate them from any generic category of clinical depression.

The aims of such a classificatory system would be to ensure that there is a shared functional language to assist both clinicians to communicate effectively and researchers to

define the conditions and samples being studied. In terms of the depressive subtypes, we would expect that they could be clinically defined and differentiated, and that their subtyping status would be supported by studies showing evidence of specific causes or a distinct differential response to treatment modalities. For all diagnostic entities, we would expect that their clinical definition had established reliability, in that two independent raters would consistently correctly classify the same individual as meeting diagnostic criteria or not.

These considerations should be kept in mind when reading the following review of the two principal systems in current use – the DSM and ICD classificatory protocols – and the discussion of other potential models of classification.

OVERVIEW OF THE PRINCIPAL CLASSIFICATION SYSTEMS CURRENTLY IN USE

The DSM system

The current DSM-IV system is based on the DSM-III classificatory system that was introduced in 1980 (American Psychiatric Association, 1980). This system was radical at the time of its introduction. Firstly, it was atheoretical in relation to cause. Secondly, it imposed a criterion-based system for diagnosis. Thirdly, it sought to bring a new standard of reliability to diagnostic decision-making and so advance psychiatry as a science-weighted discipline. However, as detailed in a book titled *The Selling of DSM: The Rhetoric of Science in Psychiatry*, Kirk and Kutchins (1992) observed that, 'It was the claims of success, however, that were successful' (p. 159). In essence, while the DSM-III architects claimed high inter-rater reliability (superior to its DSM-II predecessor), the field trial reliability studies were poorly conducted (e.g. nonblinded raters), were often not reported and the architects' standard (a kappa value of 0.70) was rarely reached. It is against this general – and generally unappreciated – background that we consider the model in terms of its reliability, validity and clinical utility.

In moving to a criterion-based system, the DSM-III working group on depressive disorders needed to consider the competing unitary and binary models. At that time – from the mid-1970s to early 1980s – those proposing a binary model had failed to provide convincing evidence to support their case. The committee effectively chose a compromise, with an initial dimensional model positioning 'major' versus 'minor' disorders. If criteria for major depression were met, categorical second-order decisions about the presence of other conditions (e.g. psychotic depression or melancholia) were specified. That broad model is also evident in the next version of the system – DSM-IV.

According to DSM-IV (American Psychiatric Association, 1994), a diagnosis of 'major depressive disorder' requires the presence of two weeks of a depressed mood, a minimum number of symptom criteria and impairment. It can be single or recurrent, and can be specified as (i) of mild severity, (ii) of moderate severity, (iii) severe without psychotic features, (iv) severe with psychotic features, (v) in partial remission, (vi) in full remission and (vii) unspecified. Other specifiers include (a) chronic, (b) with catatonic features, (c) with melancholic features, (d) with atypical features, (e) with postpartum onset and (f) being due to a general medical condition. For those with recurrent major depression, additional specifiers allow ratings of (i) with or without interepisode recovery and (ii) any seasonal

pattern. For those with bipolar disorder experiencing a depressive episode, a diagnosis of major depression with all the multiple specifiers and an additional specifier of rapid cycling is available. While cyclothymia is positioned as a fluctuating mood disorder with hypomanic symptoms, the occurrence of major depressive episodes during such an illness course alters the diagnosis to bipolar I or II disorder.

Minor disorders include dysthymic disorder and several 'not otherwise specified' conditions, including minor depressive disorder and recurrent brief depressive disorder, or depressive conditions occurring in conjunction with a general medical condition. In practice, differing depressive conditions can be concurrent, so that major depression can be superimposed on dysthymia (so-called 'double depression').

In addition, DSM-IV has a category of 'adjustment disorder with depressed mood', to be used when the predominant manifestations are symptoms such as depressed mood, tearfulness or feelings of hopelessness occurring within three months of a stress. This can be subtyped as acute or chronic. As well, there is a category of 'adjustment disorder with mixed anxiety and depressed mood'.

The DSM-IV model is therefore a mixed one. It has dimensions based on severity, persistence and recurrence. It is also semi-categorical in that the generic major depression category branches into several potential diagnostic subcategories (e.g. psychotic depression, melancholic depression, atypical depression).

In addition, it seeks to include course-of-illness variables (e.g. interepisode recovery, rapid cycling) and potential primary conditions (e.g. bipolar disorder, general medical conditions, substance-induced mood disorders). The resulting matrices (the breadth of the enterprise disallows a single matrix) are large, encompassing multiple combinations of variables, so that more than 200 diagnoses are allowed by the system.

The ICD system

The current revision of the ICD system – ICD-10 (World Health Organization, 1992) – essentially adopts a unitarian dimensional model, operating across severity, persistence and recurrence parameters. The dimensional nature of symptoms 'appearing somewhere on a line between normality and severe pathology' allow that 'it may be a matter of temper or level of sensitivity to symptoms' that decides 'whether a depressive symptom is diagnosed as present or not', with such decisions influencing the reliability of establishing a depressive episode (Bertelsen, 1999).

There are separate categories for single and for recurrent depressive disorders. For single depressive episodes, both mild and moderate expressions are subdivided into states 'with' (involving four or more symptoms) or 'without' (few or no symptoms being present) a somatic syndrome. Severe (single or recurrent) episodes are divided into those with or without psychotic symptoms, and there are categories of 'unspecified depressive episodes' and 'other (single or recurrent) depressive episodes'. The system has a separate set of persistent mood disorders, including cyclothymia and dysthymia, in addition to eight other rather diffuse categories. Dysthymia is defined, in part, as a longstanding condition (but without the DSM-IV imposition of a two-year period) and of such a low level of severity that it does not meet criteria for even a mild depressive disorder.

In addition, ICD-10 has a 'neurotic, stress-related and somatoform disorders' section, which includes 'mixed anxiety and depressive disorder' and adjustment disorders with

(i) brief depressive reaction, (ii) prolonged depressive reaction and (iii) mixed anxiety and depressive reaction. The ICD-10 system has more than 100 categories to which a depressed patient can be assigned.

CONCERNS ABOUT CURRENT CLASSIFICATORY APPROACHES

Successfully distinguishing clinical depressive conditions from normal mood states requires identification of pathological and substantive features. Ideally, these would be necessary and sufficient for a diagnosis but, unfortunately for ease of classification, no depressive symptom meets that criterion. If distinctive clinical features cannot be identified and precisely defined, any underlying categorical conditions will not be able to be identified, thereby leaving a dimensional model as the default option.

As noted, both the DSM-IV and ICD-10 systems position clinical depression as a single entity that varies dimensionally. The first difficulty associated with such a model is determining the cut-off criteria for caseness. A second problem is that case diagnoses based on these systems are commonly viewed as sufficient in and of themselves to explain cause and to shape treatment, which, as will be shown later, is not the case.

The DSM model proposes that both major and minor expressions of depression exist. There have also been many studies in the last decade arguing for an even less severe dimensional expression – variably termed 'subsyndromal' or 'subclinical' depression (Judd *et al.*, 1996). In a community sample, we found that 89 % had met criteria for those wide definitions of 'depression' by their late thirties (Parker, 2007a).

Such a high prevalence poses some questions. What do we – and what should we – mean by 'clinical' depression? Presumably, our current definition would include any condition that meets criteria for a DSM or ICD diagnosis. Although lifetime clinical depression was once viewed as a rare disorder, the great majority of the population would now meet DSM or ICD criteria for a clinical depressive episode over their lifetime. This is a consequence of diagnosis being based on a dimensional model with progressively lower cut-off criteria for caseness. As an analogy, if the diagnosis of respiratory infections was modelled in a similar manner (ranging dimensionally from a cold to pneumonia), even minor transient respiratory conditions could be viewed as requiring clinical intervention if the cut-off point for caseness was set low. Viewing clinical depression similarly as a near-universal experience strains the credulity of both the public and many clinicians, who express concerns about pathologising transient expressions of human distress.

Thus, while clinical depression was almost certainly underdiagnosed previously, there is now the contrary risk – produced by the formal classificatory systems – of overdiagnosis. Extension of the dimensional model influences epidemiological studies, in that the higher prevalence rates in recent decades could reflect a real increase or merely be an artefact of the broadened definition. More importantly, by including quite disparate expressions of depression (from slight to substantive) within broad overall categories, the causes, pathogenesis, natural history and potential differential treatment responses of the constituent conditions are effectively blended and so are resistant to dissection.

These concerns are best viewed in relation to the DSM concept of major depression. As detailed elsewhere (Parker, 2005), the initial descriptive profile of major depression within the DSM-III system effectively described the 'melancholic' subtype of depression, a condition that was previously judged to have a low lifetime prevalence (less than 5 %).

However, a DSM-III guiding principle was to have clinical criteria described at the 'lowest order of inference necessary to describe the characteristic feature of the disorder' (American Psychiatric Association, 1980, p. 7), in essence, arguing for a low cut-off and thus a risk of overdiagnosis. The relatively low number of symptom criteria, their low inference level and a relatively soft definition of mandated impairment therefore made it relatively easy to meet the definition for major depression. A lifetime prevalence of one in four women and one in six men is a common estimate for this broader definition. When community groups are reviewed at regular intervals (to overcome any forgetting of episodes) even higher estimates can be generated. For example, in the community sample of adults noted earlier (Parker, 2007a), 42 % had met lifetime criteria for major depression by their late thirties.

At first, major depression was viewed by the architects of the DSM system as describing a 'full affective syndrome'. This has progressively changed so that it is now more viewed as having the status of an entity, with papers and monographs describing *its* characteristics, while researchers pursue *its* origins and clinicians offer treatment for *it*. While studies may describe certain characteristics of major depression (e.g. mean age of onset, gender difference, mean duration of episode, patterns of persistence and recurrence, and response to differing treatments), such analyses are based on the grouped data allowed by the diagnosis – and thus its constituent subgroups with quite contrasting profiles and patterns are merged into the one overarching entity.

A diagnosis such as major depression has led increasingly to seemingly authoritative homogenising statements, whether in public destigmatisation campaigns, professional education programmes or to individual patients. For example, we are informed that major depression is a 'disease' or a 'persisting and recurrent' condition. In reality, major depression status can be achieved both by those with depressions that do and do not conform to disease status and many people who experience single and/or brief episodes. Such realities challenge any generalisation drawing on group data to characterise clinical depression and major depression.

An even greater problem – as it impacts on whether patients receive appropriate treatment – is to assume that a diagnosis of major depression is sufficient to dictate treatment choice. My personal view is that terms such as 'clinical depression' or 'major depression' are no more than domain names, just as dyspnoea describes the respiratory domain, and are logically insufficient in and of themselves to dictate any treatment option.

Let us return to analogy. For the domain of dyspnoea we allow that some individuals might be temporarily breathless due to overexertion (and therefore likely to have a spontaneous remission or benefit from some common-sense advice) and others might have other quite pathological conditions (e.g. asthma, pneumonia) and require specific and differing interventions. A diagnosis of dyspnoea is not therefore of itself sufficient to indicate the most appropriate response. Similarly, viewing major depression or any other consolidated dimensionally-based diagnosis as sufficient in and of itself to shape treatment lacks any logic.

Thus, while this chapter focuses on a number of diagnostic approaches to classifying the depressive disorders, the reader is encouraged to step back from the detail and consider the following questions. Firstly, should our classificatory systems be entirely atheoretical and ignore aetiology? Secondly, if 'depression' can exist as a disease, a syndrome, an existential state and a normal reaction, why should we expect any single model (categorical or dimensional) to be explanatory? Thirdly, if dimensional models are adopted, how valid

and useful are the criteria sets in addressing the opposing risks of underdiagnosis and overdiagnosis? Fourthly, as a consequence of their homogenising of constituent distinctive subgroups, do group diagnoses such as major depression risk providing misleading and imprecise information? Finally, if our current classificatory models have major limitations for the conduct of clinical practice and research, why are they not questioned?

HISTORICAL OVERVIEW OF CONTRASTING BINARY AND UNITARY MODELS

The binary view of depression postulates two separate types of depression (endogenous or psychotic versus neurotic or reactive) and has had an extended history. For example, Altschule (1967) has described how in the Bible, St Paul (in Corinthians) distinguished between two types of depression: one 'from God' (reflecting its otherwise inexplicable onset) and the other 'of the world' (reflecting clear causal factors).

Over the twentieth century a number of beliefs developed regarding endogenous depression (now termed 'melancholic depression', a term introduced by Hippocrates over two thousand years ago). Firstly, that its more 'inexplicable' and 'irrational' expression reflected genetic and other biological causes rather than environmental psychosocial factors. Secondly, that it had a distinctive set of so-called endogeneity symptoms and signs – as considered shortly. Thirdly, that it showed a preferential response to physical treatments, such as antidepressant drugs and electroconvulsive therapy (ECT), and was less responsive to psychotherapy.

By contrast, the second 'neurotic', 'reactive' or even 'atypical' depressive type was viewed as emerging as an interaction between a predisposing personality style and precipitating life event stressors, particularly in those with high levels of anxiety or 'neuroticism'. Individuals with this second depressive type were also 'atypical' in that – unlike those with the endogenous type – they were less likely to respond to the tricyclic antidepressants (TCAs). As they were more likely to respond to the other available antidepressant drug class – the monoamine oxidase inhibitors (MAOIs) – atypical depression was progressively modelled as a separate depressive type (Parker *et al.*, 2002), although it may have been that the suggested specificity of the MAOIs more reflected their anxiety-reducing propensities within that depressive syndrome.

In the 1920s, Mapother (1926), then medical superintendent of the Maudsley Hospital, delivered a paper arguing that distinguishing between the two types of depression was pointless as such categorical distinctions did not inform about cause, prognosis or treatment. His paper initiated the unitary view of depression in the United Kingdom. In essence, this view presupposed that there is only one type of depression, with expressions varying by severity – a dimensional model.

The introduction of multivariate statistical approaches reactivated the unitary versus binary debate in the 1960s but did not result in enlightenment, as most studies adopted factor analyses of symptoms as their key approach. Factor analysis produces dimensions rather than groupings of patients and was therefore theoretically inappropriate. In addition, while factor analysis was viewed by proponents as generating an endogenous general factor and a second factor contrasting endogenous and neurotic depression symptoms, it has since been argued (Parker and Hadzi-Pavlovic, 1996) that the general factor identified in such

studies merely represented depression severity, while the second factor more contrasted depression and anxiety than separate depressive subtypes. Subsequently, more appropriate categorical analytic strategies, such as cluster analysis and latent class analysis, were used. One of the most informative cluster analyses was undertaken by Paykel (1971). In his four-class solution, he identified a 'psychotic' cluster (comprising individuals with features typical of endogenous depression), 'anxious' and 'hostile' clusters (perhaps capturing those with nonendogenous disorders and high levels of anxiety manifested by internalising and externalising strategies respectively), and a cluster comprising young patients with a personality disorder.

In another study (Parker *et al.*, 1994), a latent class analysis of self-reported endogeneity symptoms and observer-rated signs of psychomotor disturbance identified the superiority of psychomotor signs over symptoms, with a bimodal distribution of sign scores arguing for the existence of two separate classes of depression. Validation analyses supported the differentiation of melancholic and nonmelancholic classes by the respective presence or absence of such signs of psychomotor disturbance. Nevertheless, critics have suggested that the classes or groups produced in such studies could still be determined by severity. Even if subtypes can be identified, these critics echo Mapother's earlier sentiments as to whether depressive subtyping is of any consequence (e.g. Goldney, 2006).

THE EXPLANATORY CAPACITY OF DIMENSIONAL AND SUBTYPING MODELS

The historical and contemporary challenge, 'Does subtyping matter?', is fundamental. It takes us to the heart of any consideration of the diagnosis and classification of the depressive disorders. To the unitarians, as depression is viewed as varying by degree, treatment choices are commonly decided on the basis of severity. Such a model generates treatment maxims such as 'ECT for severe depression, antidepressant drugs for moderate depression and psychotherapy for mild depression'.

The opposing argument – for conceding subtypes – was well put by Kendell (1989), who drew on historical analogies. For example, he noted that subtyping 'the pox' into two distinct syndromes – chicken pox and small pox – allowed prediction as to who would recover and who was in danger of dying, and distinguishing between cardiac and renal forms of 'dropsy' allowed prediction of those who would respond to digitalis. Another analogy can be offered. It is not particularly useful to categorise breast lumps along a severity continuum based on size. It is more important to subtype on the basis of pathology, as this is more likely to inform about aetiology and certainly more likely to assist treatment decisions. While it is theoretically possible to apply a dimensional model to managing breast lumps, it would clearly risk undertreatment of small cancerous lumps and overtreatment of large noncancerous cysts. Such analogies are worthy of respect when considering whether clinical depression is best modelled dimensionally or according to a subtyping model. However, the answer should not come from the strength or appeal of any analogy, but from a simple but more basic question: 'Which model is valid?' More specifically, do the depressive disorders best conform to a unitary, binary or arbitrary model? Examination of the current DSM and ICD systems suggests that the third model is currently in ascendance.

The limitations to working with an invalid model are many, and may be appreciated by returning to an earlier analogy. Dimensionally modelling clinical breathlessness by severity would not be informative, and would limit management. Instead of subtyping on the basis of the underlying condition – asthma/pneumonia/pulmonary embolus – and prescribing a bronchodilator/antibiotic/anticoagulant to address the respective pathological processes rationally, management would be compromised by applying a severity-based paradigm. Treatment differentiation studies would also be compromised. Imagine if a very effective bronchodilator was tested in a placebo-controlled trial of 100 subjects with clinical breathlessness – but only a couple of the subjects actually have asthma. The active drug would be unlikely to differentiate from the placebo, and the treatment would be judged as either acting as a placebo or as ineffective, when in fact if all the subjects it was tested on did have asthma the results would have been quite different. If there are depressive subtypes, such risks to research and management operate if a dimensional model is imposed.

RESEARCH AND TREATMENT DIFFICULTIES WITH CURRENT DIAGNOSES

DSM-IV diagnoses of major depression and dysthymia

The introduction to DSM-IV notes that its 'highest priority has been to provide a helpful guide to clinical practice', with the 'additional goal' being 'to facilitate research and improve communication among clinicians and researchers' (American Psychiatric Association, 1994, p. xv). Such objectives – and the extent to which they have been reached – are worthy of close focus.

The term 'major depression' has clearly been widely accepted. As detailed elsewhere (Parker, 2005), it promoted communication among practitioners and provided a frame of reference for research studies. Further, the simplicity of the concept seized the imagination of patients, doctors and lawyers, while its cachet still advances hospitalisation and medical insurance coverage. However, as already noted, major depression has accrued entity status and explanatory properties greater than the evidence supports. Post-implementation studies have found low reliability of such a diagnosis (Parker, 2007a). The diagnosis fails to meet any of the orthodox criteria for validity or to inform us about aetiological factors, and lacks diagnostic usefulness as it fails to predict prognosis and treatment outcome. As summarised by Hickie (1996), research studies of subjects with the diagnosis of major depression have 'largely failed' to 'demonstrate any coherent pattern of neurobiological changes', can't 'replicate key biological correlates across different research groups, age cohorts and treatment settings' and can't 'demonstrate any specific pattern of treatment response outside inpatient treatment settings' (p. 39).

Diagnostic utility is probably best approached by examining treatment specificity. Khan and colleagues (2002) analysed data submitted to the United States Food and Drug Administration (FDA) by the manufacturers of nine new antidepressants that gained FDA approval over 1985–2000. In only half of the 52 studies did the antidepressant drug show superiority over placebo for subjects with major depression. While the risk in interpreting such studies is of viewing antidepressants as minimally efficacious, such results are more likely to reflect randomised controlled trial procedures. The procedures effectively limit

certain clinical subpopulations (e.g. those with melancholic depression, those who are suicidal) and subpopulations with a high rate of spontaneous remission and placebo response (more likely when studies often recruit community volunteers or outpatients and rarely inpatients). Even more relevantly, as major depression is a diagnosis likely to include multiple depressive subtypes and syndromes comprising both antidepressant responders and nonresponders, the homogenising of such constituent disorders in these studies compromises true interpretation of antidepressant treatment efficacy.

Further, and as reviewed elsewhere (Parker, 2004), meta-analyses of randomised controlled trials found comparable overall efficacy levels (in the order of 50–55 %) for most treatments of major depression, including differing antidepressant drug classes and differing principal psychotherapies. Studies comparing antidepressant drugs and psychotherapies found similar efficacy rates, and even less orthodox treatments such as St John's Wort showed similar efficacy to formal antidepressants.

A nonspecific diagnosis must be expected to risk nonspecific results in relation to causes, outcomes and treatment differentiation. Thus, while widely accepted as an entity, the nonspecificity of a diagnosis of major depression has retarded pursuit of specific causes of the depressive disorders and led to nondifferentiating treatment outcomes. As multiple strategies can be viewed as equally effective because of the issue of diagnosis, treatment is often dictated by secondary factors – commonly influenced by the professional's background discipline and training rather than the therapy being 'fitted' to the particular depressive disorder. This is not only discordant with the medical model but lacking in common sense.

While the DSM category of dysthymia has never achieved quite the same status as major depression, the criticisms already noted apply equally to this term. Dysthymia homogenises a group of less severe but more chronic conditions within a nonspecific category. Thus, as argued earlier, diagnoses such as major depression and dysthymia do no more than identify a clinical domain – depression – as might clinical dyspnoea inform us about another domain – breathlessness. Such diagnoses are not sufficient in and of themselves to inform us about cause and outcome. They are better viewed as first-stage estimates of the probability of clinical depression that invite more fine-focused diagnostic subtyping. Whether the DSM categorical specifiers meet that secondary need is the next issue considered.

Definition and utility of key DSM categorical specifiers

As several of the DSM specifier categories seek to capture depressive subtypes, their definition and criteria sets are important.

Perhaps the most important category is the *with melancholic features* specifier. As noted earlier, the binary view of depression positioned endogenous depression ('melancholia') as a separate and categorical type, reflecting biological determinants, defined by certain endogeneity symptoms and showing a preferential response to physical treatments.

Operational concerns emerged early in relation to DSM-III criteria for melancholia. Zimmerman and colleagues (1989) observed that in comparison to DSM-II the DSM-III melancholia criteria set 'did not predict treatment response'. As a consequence, in the DSM-III-R (American Psychiatric Association, 1987) the criteria set for melancholia was revised to include nonsymptom criteria (e.g. interepisode recovery, previous response to physical treatments and absence of any personality disturbance). However, the DSM-IV definition of melancholia returned largely to the DSM-III criteria set.

On the face of it, there appear to be two principal concerns about the DSM-IV criteria for melancholia. Firstly – and of principal relevance – there is little differentiation from the criteria for major depression, with five of the eight criteria for diagnosis of melancholia essentially being repeats of those for major depression. For example, consider the following (abbreviated) DSM-IV criteria for major depression and melancholia respectively: (i) diminished pleasure versus lack of pleasure, (ii) early morning wakening versus insomnia, (iii) psychomotor agitation or retardation versus psychomotor retardation or agitation, (iv) feeling worthless or excessive or inappropriate guilt versus excessive or inappropriate guilt and (v) significant weight loss versus significant anorexia or weight loss. In fact, there are only three nonshared DSM-IV criteria for melancholia (i.e. mood nonreactivity, mood worse in mornings, distinct quality of mood), and as none are mandatory, and not all listed criteria for melancholia are required to meet diagnostic status, differentiation from major depression is further minimised. Thus, an individual who had the following five criteria – anhedonic mood, early morning wakening, psychomotor disturbance, weight loss and excessive or inappropriate guilt – would meet symptom criteria for *both* major depression and melancholia.

If melancholia is – as the DSM model operates – a subordinate category of major depression, then there is no theoretical need for any clinical feature to be repeated in the criteria for classification. If melancholia is a depressive subtype, then logic would suggest that its definition – once criteria for major depression are met – would require the presence of one or more clinical features that are specific to melancholia (and which, conversely, do not contribute to the definition of major depression). The overlap between major depression and melancholia in the DSM-IV criteria sets is large, however. This definitional limitation challenges logic but, more importantly, prevents (or at least limits) determining if melancholia has specific causes or treatment responses that differentiate it from those in the overall major depression class.

A second concern about the DSM-IV clinical definition of melancholia is that some of the symptoms lack precision. One ('excessive or inappropriate guilt') could range in practice from an individual feeling very guilty about not meeting family or work commitments while unwell (common but not clinically significant) through to an overvalued idea or a delusion that might be specific to psychotic depression. For those who rate positive on such an item it is impossible subsequently to determine the nature of their affirmation and any potential specificity to the item is lost by its diffuse expression. Another melancholia criterion, 'distinct quality of depressed mood', is defined as different from feelings 'experienced after the death of a loved one'. This is a negative definition, akin to defining soccer as 'not baseball'. Without any positive definition, its nonspecificity risks error, as has been demonstrated (Parker *et al.*, 1997a).

As a consequence of such limitations, both aetiological and treatment studies of those with DSM-IV-defined melancholia have failed to generate any substantive support for its specificity as a category. As argued, this is to be expected if its definitional separation from major depression is minimal. The oversimplified features, the low threshold of many symptoms and the absence of specific features argue the need for a change to the DSM melancholia criteria (Taylor and Fink, 2006).

A second key category is the *atypical features* specifier. As reviewed elsewhere (Parker, 2007b), 'atypical depression' has evolved historically: initially as a residual category in comparison to 'endogenous depression', then to an anxiety-weighted condition, then to a personality-weighted condition of 'hysteroid dysphoria' and then to a spectrum disorder

comprising personality as well as depressive symptom criteria. As currently defined in DSM-IV it is not a rare condition, with quantitative studies (Parker, 2007b) suggesting a prevalence of up to two-thirds of depressed outpatients. The DSM-IV criteria mandate mood reactivity and two or more of four secondary criteria (appetite and/or weight gain, hypersomnia, leaden paralysis and a personality style of rejection sensitivity). However, two independent studies (Parker *et al.*, 2002; Posternak and Zimmerman, 2002) have challenged the primacy of mood reactivity as a mandatory or defining feature and found minimal associations between constituent features – so arguing against its status as a syndrome. The former study argued the primacy of personality style (specifically 'rejection sensitivity') and suggested that some of atypical depression's criteria (e.g. hyperphagia, hypersomnolence) may be more coping repertoires. The longstanding argument that atypical depression is a specific depressive subtype because of a preferential response to MAOI antidepressants is no longer sustainable, with both selective serotonin reuptake inhibitor (SSRI) antidepressants and cognitive behaviour therapy shown to be beneficial.

A third category to consider is *psychotic depression*. In DSM-III, psychotic depression was a subset of major depression. 'Major depression with psychotic features' was to be used when delusions or hallucinations were present or when there was depressive stupor ('the individual is mute and unresponsive'). While depressive stupor may be a useful marker or proxy for the condition, this criterion was not retained in DSM-III-R or DSM-IV (but is included in ICD-10). Classification of psychotic depression in DSM-IV is both dimensional and categorical, in that only 'severe' major depression can be coded as associated with the presence or absence of either delusions or hallucinations. While psychotic depression is, almost by definition, a severe mood state (Parker *et al.*, 1991, 1997b), and psychotic features usually disappear as the depressed mood abates with treatment, some patients report continuing psychotic symptoms in conjunction with moderate or mild depression. While diagnosing them at the nadir of their depressive episode would overcome this DSM nuance, the diagnostic status of such patients when psychotic features remain in conjunction with a milder level of depression is problematic.

ICD-10 diagnoses

Limitations created by the dimensional model underpinning classification of the depressive disorders in the DSM system are also evident in the ICD-10 system.

The ICD-10 system (World Health Organization, 1992) was published after 15 years of preparation. The chapter on the classification of mental disorders was constructed after a series of field trials were undertaken and is well described by Sartorius and colleagues (1993). The objectives of these field trials were to test the reliability of the classification and the acceptability of the diagnostic formulations to those who would use the system: the trials did not aim to assess the validity of the system.

The development, aims, structure and use of the chapter on mental disorders in the ICD-10 system has been overviewed by Dilling (2000). As the classification was to be used worldwide, it needed to be acceptable and understandable across regions and cultures. It was designed to be 'versatile', with differing versions for different users and purposes. It was published as a family of documents, including the 'Blue Book' (containing the Clinical Descriptions and Diagnostic Guidelines), the 'Green Book' (containing the Diagnostic Criteria for Research), a multiaxial version and a primary health care version. However, the documents do not always link cohesively. For example**,** the ICD-10 diagnostic guidelines

and research criteria for mood disorders are not identical. Moderate or severe depressive episodes are defined by the number of symptoms alone according to the research criteria, while the diagnostic guidelines also consider the severity of symptoms.

The introduction to the ICD-10 system for diagnosing mood disorders is somewhat apologetic. It acknowledges that relationships between causes, underlying biological processes, treatment response and outcome are not well understood but nevertheless 'a classification must be attempted'. There is an appeal to the reader that what is presented will 'at least be acceptable, since it is the result of widespread consultation'. It alludes to certain 'somatic' symptoms (which could also have been called 'melancholic', 'vital', 'biological' or 'endogenomorphic') and adds a caveat that 'the scientific status of this syndrome is in any case somewhat questionable'. Consequently, we are informed that this 'classification is arranged so that this somatic syndrome can be recorded by those who so wish, but can be ignored without loss of any other information'. Thus, the reader observes a formal diagnostic system with an arbitrary component. The so-called somatic symptoms correspond broadly to DSM-IV melancholia specifier criteria – albeit without the vague 'distinct quality' criterion and the criterion of 'excessive or inappropriate guilt'.

The reader is left with the view that what has been derived largely reflects committee decision-making and that contentious issues (i.e. to include melancholia or not) are resolved by a 'take it or leave it' option. Further, the implication is that while the ICD-10 criteria – and classification per se – may have many limitations, the use of available evidence, the high level of expertise of the consultative committees and the widespread consultation should be sufficient to encourage its use.

Dilling (2000) has summarised differences between ICD-9 and ICD-10 classifications of mood disorders. In ICD-9 'endogenous depression' and 'neurotic depression' were differentiated. However, neurotic depression is no longer found in ICD-10. Although most of those cases are coded as dysthymia, Dilling noted that there were no fixed rules for applying such a diagnosis. Dilling also observed the practical difficulties associated with differentiating between mild, moderate and severe depressive disorders. While the structure resembles DSM-IV, Dilling commented that each system imposes differing grades of severity in making such diagnoses, so that (for example) dysthymia in one system is not necessarily dysthymia in the other.

In terms of its utility, ICD-10 diagnostic options are far less commonly used in research studies. Finally, its dimensional basis generates the same problems previously detailed in relation to the DSM system. For example, formal testing of its reliability has identified several concerns. Hiller *et al.* (1993) studied a sample of psychiatric patients with psychotic disorders and depressive conditions. Inter-rater diagnostic reliability was acceptable across the whole sample (kappa = 0.82), but 'poor' if restricted to the depressive subsample (kappa = 0.40), suggesting greater imprecision in diagnosing dimensionally-based conditions than categorical states (such as psychosis). More specifically on this point, the authors noted that their data were discouraging for differentiation of mild, moderate and severe depressive episodes.

PSYCHIATRY IS NOT ALONE

The extended unitary versus binary debate presumed *either* that there were two categorical conditions *or* that depressive disorders varied dimensionally. As noted elsewhere (Sartorius

et al., 1993), it is in our nature as human beings to seek the simplest models, and if a simple taxonomy did have explanatory power we would all be most appreciative. The expectations set for a binary model were unrealistic, however, in that it was 'unwise to expect the precision of a Linnean botanical binomial taxonomy' (Parker and Manicavasagar, 2005). As detailed by Bryson (2003), pre-Linnaeus botany had 'a highly whimsical' classificatory system. Bryson notes a number of botany's binary models (e.g. wild versus domesticated, terrestrial versus aquatic, large or small), but 'even today there is more disorder in the system than most people realize', with the estimates of the number of phyla ranging from the low 20s to high 80s, and with models also dependent on whether the biologists are 'lumpers' or 'splitters' (pp. 316–317). Bryson again: 'In principle, you ought to be able to go to experts in each area of specialisation, ask how many species there are in their fields, then add the totals. Many people have in fact done so. The problem here is that seldom do any two come up with matching figures' (p. 321). A similar classificatory dilemma exists in palaeontology. Altogether, 'some twenty types of hominid are recognised in the literature today. Unfortunately, almost no two experts recognise the same twenty', and 'The only way a name becomes accepted is by consensus, and there is often very little of that' (p. 389).

Thus, psychiatry is not alone and, as we have argued elsewhere (Parker and Manicavasagar, 2005), the task involved in modelling depression is more in tune with interpretive anthropology where respect is given to 'thick description'. In anthropology, this approach seeks to go beyond describing the behaviour to incorporate the context in which it occurs. In psychiatric classification, it would involve defining clinical patterns or phenotypes (precisely or approximately) and, ideally, including or considering their aetiologies. The next section considers how such a process might proceed.

AN ALTERNATIVE MODEL: A SUBTYPING APPROACH RESPECTING CAUSE

An alternative model proposes that there may be one or more categories or types of depression but that not all depressive syndromes can be constrained as categorical entities. If valid, it necessitates multiple models.

Assuming that categorical depressive conditions exist, the key candidates would appear to be melancholic and psychotic depression – melancholia because of its lengthy status and ascriptions, and psychotic depression because it has a categorical feature (i.e. psychosis) absent in nonpsychotic depressive disorders.

In a thought-provoking paper titled 'Striving for coherence: psychiatry's efforts over classification', McHugh (2005) addressed what he described as psychiatry's 'most obstinate challenge – how to bring its diagnoses and explanations together'. He suggested that since 1980, and while the DSM manual has gone through several revisions, it was time to complain as, 'Quite simply, the process got out of hand'. In essence, the DSM decision trees 'enhance accuracy of identification' but they 'do not explain distinctions'. McHugh argued that the situation faced by psychiatry today is remarkably similar to the situation faced by physicians in the nineteenth century and 'susceptible to a similar solution'. Then, physicians identified patients from appearances and tentatively explained their conditions by 'the [a]etiopathic ... agencies comprehended at the time'. He counselled that while psychiatrists have not taken such a synthesising step, eventually they must.

McHugh argued the advantage of identifying aetiopathic clusters. He formulated four clusters, three of which are relevant to a subtyping classification of depressive disorders and described below.

Cluster A comprises 'brain diseases that directly disrupt neural underpinnings of psychological faculties'. Psychotic and melancholic depression would appear to be two key candidates for this cluster (conditions that constituted endogenous depression in the old binary model).

Cluster B describes those 'vulnerable to mental unrest because of their psychological make-up'. Here we could envisage those with nonmelancholic disorders principally contributed to by the individual's temperament or personality style – neurotic depression in the old binary model.

Cluster C describes those with 'distressing mental conditions provoking events thwarting and endangering their hopes'. Here we could position those with nonmelancholic disorders contributed to by stress – reactive depression in the old binary model.

McHugh concluded that, despite reliable definition, a symptom-based approach is insufficient for full understanding of a patient and that aetiopathic clustering is the next most logical organising step.

ANOTHER ALTERNATIVE: A MIXED SUBTYPING APPROACH

The model

Personal research (Parker, 2007c) will now be reviewed to consider the utility of an alternative mixed model. This model views 'melancholic' and 'psychotic' depression as categorical conditions capable of being distinguished from a heterogeneous residue of 'nonmelancholic' depression. The latter, lacking specific features, requires dimensional modelling.

Despite controversies over its status and classification, the rationale for a diagnostic category of melancholia (Parker and Hadzi-Pavlovic, 1996; American Psychiatric Association, 1987) includes (a) a greater relevance of genetic and other biological causes than psychosocial causes, (b) evidence of disturbance in biological functioning, especially of the hypothalamic–pituitary–adrenal axis, (c) a superior response to physical treatments such as antidepressant drugs and ECT (compared to the psychotherapies), (d) a low placebo response rate and (e) a distinctive pattern of symptoms and signs.

Presuming that melancholia exists as an entity, the next question is how best to define it. Any such objective is immediately constrained by the reality that symptoms of depressive disorders – as for many medical disorders – are intrinsically imprecise, lacking in specificity and subject to numerous self-reporting rating biases. While many endogeneity symptoms have been historically suggested as markers of melancholia (including appetite and weight loss, terminal insomnia, diurnal variation of mood and energy, nonreactive and anhedonic mood), several studies (Parker and Hadzi-Pavlovic, 1996; Nelson and Charney, 1981; Rush and Weissenburger, 1994) indicate that they are also common in other depressive disorders. They are thus insufficiently specific to delineate, define and discriminate melancholia with acceptable precision. More specific symptoms (e.g. abulia – an inability to feel anything) may have greater specificity but as rare clinical features in melancholia do not assist the general task.

Because of such limitations to a symptom-based approach, we have argued elsewhere (Parker and Hadzi-Pavlovic, 1996) for observable psychomotor disturbance (PMD) as a specific and discriminating feature and developed a measure to capture its constituent features. This 'CORE' measure has three scales – a central 'noninteractiveness' scale which captures cognitive processing difficulties (e.g. poor concentration) and two motoric scales defining 'retardation' and 'agitation' items. We demonstrated the superiority of the CORE (over assessment of endogeneity symptoms) in measuring the probability of melancholic depression in a series of studies (Parker and Hadzi-Pavlovic, 1996). Further, the studies indicated that the CORE measure allowed melancholia to be defined largely by the presence or absence of observable PMD, in that discrimination was not improved by the addition of any historically favoured endogeneity symptom. Thus, as used, PMD appeared both necessary to the definition of melancholia and largely sufficient in and of itself – at least during a depressive episode. We validated this approach by demonstrating that depressed patients with higher CORE scores (i) were less likely to report earlier or precipitating life events, (ii) had compromised reaction time (as against no impairment in those with nonmelancholic disorders), (iii) had higher dexamethasone nonsuppression rates, (iv) had a higher rate of brain imaging abnormalities (e.g. volumetric reduction of the basal ganglia, hyperintensities and decreased blood flow diffusion in the dorsolateral prefrontal region) and (v) had compromised dopamine metabolism as measured by CSF HVA analyses.

These findings allowed several working hypotheses. Firstly, as clinical features are simply the surface (or recordable) markers of underlying neuropathological processes, we hypothesised that the CORE measure allows identification of neurobiologically discrete groups, akin to McHugh's (2005) Cluster A typology. Secondly, findings hint at the likely site of the neurobiological perturbations and/or lesions contributing to melancholic depression. We therefore proposed that melancholia could be modelled as a brain circuit disease. In essence, if neural networks linking the prefrontal cortex to the basal ganglia are functionally and/or structurally perturbed, this will lead to a triad of depression, cognitive impairment and observable psychomotor disturbance. Such a model is not dissimilar to that implicated in Parkinson's disease. It emphasises neurotransmitter perturbation as the principal pathogenic cause and thus argues the need for physical treatments (e.g. antidepressant drugs and ECT) as primary treatments.

The status of psychotic or delusional depression remains unclear, with debate about whether it represents a more severe expression of melancholia or a separate depressive subtype. 'Psychotic' and 'endogenous' depression were used as synonymous terms by proponents of both the binary (Kiloh *et al.*, 1971) and the unitary (Kendell, 1976) views of depression classification. An early separatist view was put by Maudsley (1895) who distinguished between 'melancholia' and 'melancholia with delusions'. Phenomenologically, the respective absence or presence of psychotic features appears to support a separate depressive subtype. Two meta-analyses examining treatment response give further support to this position. Those with psychotic depression had a 25 % chance of responding to an antidepressant alone, 30–40 % to an antipsychotic alone and about 80 % to the combination of those two drugs or to ECT (Spiker *et al.*, 1985; Parker *et al.*, 1992).

Two phenomenological studies found that those with psychotic depression generally had psychotic features in addition to severe levels of PMD, but the latter could if particularly severe render the patient near-catatonic and compromise the eliciting of psychotic features during episode nadir (Parker, Hickie and Hadzi-Pavlovic, 1996). Multivariate analyses indicated that a diagnosis of psychotic depression was supported by distinctly more severe PMD than observed in nonpsychotic melancholia and by the presence of overvalued ideas

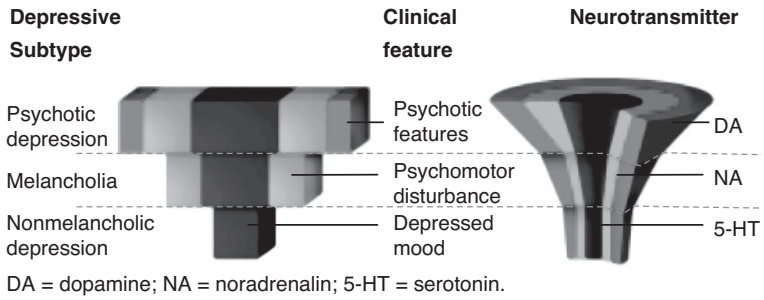

Figure 1.1 Structural and functional model of three depressive classes. (Reproduced by permission, from G. Parker and V. Manicavasagar (2005) *Modelling and Managing the Depressive Disorders*, Cambridge, UK: Cambridge University Press)

or morbid cognitions (particularly focusing on guilt and punishment), the absence of any diurnal variation in mood or energy (the subject being depressed without relief across the day) and 'constipation' or 'costiveness' (slowed in action and ideas, difficulty expressing oneself) prior to any psychotropic medication.

Such studies allowed us to develop a tiered or hierarchical model for the three principal depressive subtypes (see Figure 1.1). The structural model (left side of Figure 1.1) illustrates the central depressive mood component, which is most severe in psychotic depression, not as severe in melancholic depression and less severe again in nonmelancholic depression. However, unlike any dimensional model of the depressive disorders, the 'depressive' component is not given any distinct weighting for classification because it lacks specificity. Instead, the three classes are distinguished by the presence or absence of two categorical features. Melancholia is distinguished from nonmelancholic depression by the presence of distinct PMD, and while PMD is more severe in psychotic depression, the latter is differentiated from melancholic depression by the presence of psychotic features.

We do not view nonmelancholic depression as representing a categorical class as it has no specific features. Many of its historically ascribed features are merely the converse of melancholic expressions (e.g. mood reactivity versus a nonreactive mood), while none have any specificity to the overall residual nonmelancholic class. How then to model such heterogeneity?

Here we argue for dimensional weighting of contributory stressors and/or personality styles (Parker *et al.*, 1997b). We envisage acute and chronic stress-induced nonmelancholic disorders. The stressors act to induce depression by their psychosocial impact on the individual's base self-esteem level. For the acute ('reactive') conditions we also argue the relevance of a key and lock model, where the salience (or meaning to the individual) of the stressor may be more important than its objectively judged severity (Parker *et al.*, 1998). For example, an individual may only become depressed when criticised by an authoritarian figure (with that 'key' opening a developmental 'lock' created by extended exposure to a critical and judgemental parent). For the acute disorders the stressor is often more abrupt and less persistent (e.g. the break-up of an intimate relationship) than for the chronic disorders, where the stressor is more likely to persist and continue to have an impact on the recipient's self-esteem. Here we presume that the stressor induces a learned helplessness mindset: the individual believes that whatever they do will have no impact on outcome and thus may develop a sense of powerlessness, along with depressive symptoms.

For other nonmelancholic disorders we argue the greater relevance of certain predisposing temperament or personality styles (e.g. anxious worrying, sensitivity to rejection, perfectionism, social avoidance) (Parker *et al.*, 1997b). For many (if not most) nonmelancholic disorders, both stressors *and* personality styles contribute – a psychosocial 'stress diathesis' model. Further, for such composite states, we have pursued a 'spectrum' model (Parker and Crawford, 2007). This model supposes that certain personality styles – in response to depressogenic stressors – dispose to onset of a depressive disorder and shape the clinical pattern of symptoms and coping responses. For example, those with high trait internalised anxiety will present with an 'anxious worrying' nonmelancholic depressive episode; those with high trait externalised anxiety will present with an 'irritable' nonmelancholic depression; those with a 'self-focused' angry and entitled personality style will present with a 'hostile' nonmelancholic depression; and those with a personality style of 'sensitivity to rejection' will present with a cognitive style of feeling abandoned and rejected and adopt a series of self-consolatory behaviours (e.g. overeating, shopping, crying).

Such a model expands Paykel's cluster analysis noted earlier, where in addition to a psychotic or melancholic class, Paykel (1971) identified nonpsychotic and putatively nonmelancholic anxious and hostile depressive clusters. Several earlier studies used similar descriptors. Blashfield and Morey (1979) reviewed 11 cluster analytic studies suggesting separate anxious and hostile depressive subgroups. Further, in an extensive review of the then-published studies, Roth and Barnes (1981) suggested three principal subgroups, including depression associated with a personality disorder in addition to hostile depression and anxious depression. While such hostile and anxious subgroups have long been identified, clear and consistent descriptions are lacking. Grinker and colleagues (1961) described those with hostile depression as unappreciative, actively angry, provocative and making excessive demands of – and complaints about – their therapists, suggesting a personality disorder contribution. The anxiety subgroup is variably interpreted as including either those with an anxious personality or temperament, or those with significant anxiety symptoms that occur when depressed.

Thus, the nonmelancholic disorders are modelled as reflecting a blend of dimensional stressor and personality factors acting to diminish the individual's self-esteem. These disorders are heterogeneous; they possess no specific clinical feature and so cannot be viewed as comprising a pure 'class'.

The right side of Figure 1.1 shows a functional model that is aligned to our structural model. It assumes that if there is any neurotransmitter contribution to the nonmelancholic disorders it will principally be associated with serotonin. For melancholia we assume a greater noradrenergic contribution and for psychotic depression a greater dopaminergic contribution.

If the functional model is valid, we expect that (i) psychotic depression will require strategies affecting dopaminergic neurotransmission and (ii) those with melancholia will show a preferential response to physical treatments and a superior response to dual-action antidepressants (affecting serotonergic and noradrenergic neurotransmission) in comparison with SSRIs. Further, we predict that within the nonmelancholic class (iii) broader-action antidepressants will not have any advantage over narrow-action SSRIs and (iv) there will be no evidence of treatment modality differentiation. Each of these hypotheses is considered in turn.

As already noted, evidence supports the superiority of ECT and the combination of antidepressant and antipsychotic drugs compared to antidepressant drugs alone in psychotic depression (Spiker *et al.*, 1985; Parker *et al.*, 1992). Several studies testing the capacity

of CORE-defined melancholia to predict physical treatment response also support the hypothesis. For example, Hickie, Parsonage and Parker (1990) demonstrated that high CORE scores predicted a superior response to ECT. As well, in separate double-blind studies, the Danish University Antidepressant Group (DUAG) reported that the TCA clomipramine was distinctly superior for those with melancholia over two SSRIs – citalopram in one study (Danish University Antidepressant Group, 1986) and paroxetine (Danish University Antidepressant Group, 1990) in the other.

We have also undertaken prospective and retrospective studies investigating differential class responses to targeted treatments. A prospective study of 182 patients examined response rates over 12 months to tailored treatment options (Parker *et al.*, 2001). Four different strategies were used to assign people to melancholic and nonmelancholic groups. Those assigned as melancholic (i.e. returning a CORE score of 8 or more) were less likely than those assigned as nonmelancholic to respond to a narrow-action SSRI (23 % versus 30 %) and, conversely, tended to be more likely to respond to broad-action TCAs (43 % versus 29 %). In a retrospective clinical panel study of 341 nonpsychotically depressed patients, clinician-rated data quantifying improvement with differing previous antidepressant drugs were analysed (Parker *et al.*, 1999). Melancholic and nonmelancholic depressive groups were distinguished in one part of the study by a cluster analysis, with CORE scores (respectively 16.4 and 4.1) contributing to their selection. The TCAs and SSRIs had comparable effectiveness scores (0.98 and 0.94) for those with nonmelancholic depression. For those with assigned melancholia, however, the TCAs were nearly twice as likely as the SSRIs to be reported as effective (1.25 versus 0.70). While SSRI effectiveness appeared to decline distinctly with age in those with melancholia (here selecting on DSM-IV criteria), TCA effectiveness appeared uninfluenced by age and depressive subtype (Parker, 2002).

A superior response by those with melancholia to a broader-action antidepressant in our studies is consistent with the DUAG studies and with looser observations over earlier years that those with severe depression or hospitalised depressives (conditions possibly reflecting a greater likelihood of melancholia) were more likely to benefit from a TCA.

In another analysis we amalgamated two large clinical databases comprising 124 depressed subjects meeting DSM-III-R and clinical criteria for melancholia and contrasted them with 218 residual nonmelancholic depressed subjects [54]. We assessed PMD by the CORE measure. Next, we rated individuals on seven classical endogeneity symptoms of melancholia to create a summed 'ENDOG' score. ENDOG scores did not vary with age in either the melancholic or nonmelancholic subjects (with $r = 0.08$ and 0.04 respectively). Total CORE scores, however, showed a differential pattern. As age increased, CORE scores increased in the melancholic group ($r = 0.31$) but not in the nonmelancholic group ($r = 0.03$).

These studies suggest several possible interpretations. Firstly, that melancholia is better defined by observable PMD than by the so-called endogeneity symptoms. Secondly, that the phenotypic picture of melancholia changes with age and that these changes are better able to be detected by CORE-rated PMD than by classical endogeneity symptoms. Thirdly, that as the phenotype is likely to be influenced by disturbed biological systems and the phenotypic picture of melancholia changes with age (i.e. PMD increases), this age phenomenon might reflect recruitment of more monoaminergic systems. Specifically, we hypothesised that as an individual with true melancholia ages there may be a greater recruitment of noradrenergic and dopaminergic pathways. This may result in more distinctly observable PMD and contribute to a progressively decreasing response to narrow-action SSRI antidepressants, arguing for trials of broader-spectrum antidepressants.

In relation to the nonmelancholic class, no clear evidence base of constituent nonmelancholic disorders can be examined to test directly or validate the model outlined here. As the model has treatment implications, testing the causal hypotheses might offer a research strategy. This might involve defining nonmelancholic subsets with specific causes and appropriate corrective strategies for each group being formulated. Those with acute reactive conditions might best respond to interventions that neutralise the stressor or assist the individual to come to terms with it; those with a predisposing personality style marked by false self-attributions might best benefit from a cognitive therapy addressing the cognitive distortions; and those with a predisposing shy and unassertive personality style, making them vulnerable to exploitation and depression, might best benefit from a behaviour therapy. An aetiological–treatment matrix could then be derived, and individuals in differing cells assigned to receive either the treatment designed to address the specific causal factor or an alternative treatment.

How the model might be used in clinical practice

A sequential model is presented for consideration.

Step 1. Is a depressive disorder present?

While some patients with a melancholic or psychotic depression may deny depression or focus on somatic symptoms such as pain ('corporisation'), direct questioning (Do you feel depressed?, Has there been any drop in your self-esteem or sense of self-worth?, Are you being more self-critical than usual?) will usually elicit a depressed mood.

To determine if the depression is sufficiently severe to warrant case status, the clinician might ask about representative symptoms (e.g. amotivation, loss of interest or pleasure, feelings of worthlessness or guilt, recurrent thoughts of death and suicidal ideation, and appetite, weight and sleep changes). Secondly, the depressed mood should either have been present for at least two weeks or, if very recent, of distinct severity. It should be impairing in the sense that the individual is either unable to work or, if working at home or away, finds that performance is compromised.

At this stage, a differential diagnosis should be considered. Specifically, is the picture phenomenologically one of depression or more of grief or anxiety? Is there any higher-order psychiatric condition (e.g. schizophrenia)? Is there any medical condition that might otherwise explain certain features (e.g. fatigue being more due to anaemia or sleep apnoea)? Are there significant co-morbidities (e.g. anxiety disorders, drug and alcohol issues)?

Step 2. If a depressive disorder is established, what is its likely subtype?

While this review focuses on depressive disorders, a key assessment task when any individual presents with depression is to investigate whether the longitudinal course is unipolar or bipolar. If unipolar, our three-class hierarchical model (i.e. psychotic, melancholic and a heterogeneous nonmelancholic class) only requires clarification as to whether two class-defining specific features (psychosis and overt PMD) are present or not.

Observable PMD (the key marker of melancholia) is often evidenced by the patient showing retardation (e.g. monosyllabic talk, poverty of ideation, a nonreactive face, moving slowly) and/or agitation (e.g. slow wringing of the hands, a furrowed brow, an importuning coda of 'What's going to become of me?' or, in their agitation, repetitively voicing their worries and being resistant to reassurance). If signs of PMD are not clearly evident – or if the patient is not at episode nadir – then the following questions about symptoms appear to have greater specificity: Do you find it hard to get out of bed to have a bath or shower in the morning?, Do you feel a real lack of energy?, Is your energy and mood level worse in the mornings and does it improve as the day goes on?, Is it hard to look forward to things?, Is it impossible to be cheered up or are you cheered up only briefly?, Do you feel that your concentration is distinctly affected – as if your brain is not actually ticking over?

If melancholia appears likely on the basis of responses to such questions, then subsidiary questions pursuing a psychotic subtype are appropriate. Direct questioning about delusions, hallucinations and overvalued ideas may be helpful. If not, pursuing guilt is often useful, as the individual might be ruminating about minor past indiscretions. Questions should investigate the nature of any guilt and whether the individual believes that they are being – or deserve to be – punished. Severe PMD may falsely suggest a dementia (sometimes termed a 'pseudo-dementia') in those with psychotic depression. A percentage of individuals with primary melancholic and psychotic depression may have an organic contribution. This argues for cognitive testing.

If psychotic depression and melancholic depression are excluded, then a nonmelancholic disorder is likely as the default option, but should be supported by negative responses to all or most earlier questions. In this case, the individual will generally describe or exhibit mood reactivity, show a normal level of 'light in the eyes' during the interview and not describe any distinct psychomotor symptoms. If it is nonmelancholic depression, the interviewer should review the respective significance of any compelling distal (e.g. childhood sexual abuse, deprivational parenting) and proximal (e.g. loss of employment) antecedent stressors, and assess personality style to determine any likely contribution to a stress–personality diathesis model. Subtyping decisions often benefit from corroborative witness reports and clinical observation over time or, if the patient is admitted, from nursing staff observation.

Even when the depressive subtype has been established, further questioning should consider whether depression is the primary disorder or secondary to concomitant medical problems, licit or illicit drugs, alcohol excess, central nervous system disease or other psychiatric conditions (e.g. anxiety states, personality style or personality disorder). Here clinical judgement may adopt either a hierarchical or sequential approach. The former weights the more severe disorder as the primary condition, while the sequential approach weights the antecedent condition as primary. While, logically, management might be expected to prioritise the causal factor, this is not always relevant in clinical practice. For example, if an individual presents with a nonmelancholic depressive disorder reflecting stressors impacting on an 'anxious worrying' personality style, the patient's priority is to be relieved of the depression and of the stressors – so attention to the predisposing aetiological driver (i.e. the anxious worrying personality style) could well be included in the later maintenance phase of management.

The point to note here is that formulating a management plan can never be constructed from a diagnosis alone. The latter may provide a macro template but the components, their prioritising and their sequencing all require sophisticated clinician-based evaluation and – at the end of that assessment – a formulation.

This chapter argues against homogenising potentially quite different depressive conditions under any single diagnostic label, be it 'major depression', 'clinical depression' or some equivalent. It argues instead for a subtyping diagnostic model, which respects both phenomenological description (when it is informative) and aetiological causes and, at times (as for melancholia), argues for their interdependence. As a mixed model, it argues for psychotic depression and melancholic depression as categorical types, capable of phenotypic delineation, and offers a cause-weighted, dimensional diathesis–stress model for the residual nonmelancholic syndromes that resist clear phenomenological differentiation from each other.

SUMMARY

Consistent evidence

While current DSM and ICD systems each provide a model for diagnosis of depression, we lack consistent evidence that their constituent disorders inform us about specific causes or differential treatment options.

Incomplete evidence

There is support for psychotic and melancholic depression as categorical entities, with differing phenomenological patterns and differential responses to treatment modalities. However, current DSM-IV and ICD-10 definitions of melancholia are limited, providing minimal differentiation from generically defined major depression and with few specific defining features.

Areas still open to research

The DSM system is far less reliable than is generally realised, and while the current formal systems of diagnosis give us a shared language the underlying models are unlikely to be valid.

Present classificatory systems have low utility in terms of informing us about cause and treatment options. The chapter provides summary information about this. In contrast, it provides a more detailed review of evidence supporting the argument that a diagnosis of 'melancholia' may necessitate certain treatment-specific options (e.g. ranking a physical treatment above a psychotherapy, a broad-spectrum antidepressant above a narrow-spectrum antidepressant).

While current classifications have major limitations, psychiatry is not alone. Similar problems are described in botany and palaeontology. Such similarities are worthy of interpretation. Faced with an intrinsic need to classify, we look for simple taxonomies that have explanatory power. As a consequence we tend to seek a single model that will apply across complex data sets. We should remember Benchley's observation – there are two classes of people in the world: those who divide the world into two classes and those who do not.

The nature of the fields that might contribute to classification of the depressive disorders are diffuse and, at times, indefinable. They can encompass state and trait characteristics, symptoms, coping repertoires and underlying personality styles and be shaped and reshaped by distal and proximal stressors as well as by co-morbid and confounding factors. We lack any laboratory test or gold standard for validation or external referencing. Basically, we deal with 'fuzzy sets'. Anthropologists address such data by a matching thick description approach, as once did psychiatry with its more descriptive approach to depressive disorder delineation. Historical application of a single explanatory model to the diagnosis of depressive disorders (whether a binary model or a dimensional unitary model) is flawed, and we should consider why. In essence, if clinical depression comprises both categorical entities and noncategorical entities, a single overarching model should not be expected nor imposed. Yet, in proposing an alternative model there is a risk of moving beyond a unitary or binary debate to new models that again risk being arbitrary, as has occurred so commonly in the past. However, as McHugh (2005) has argued, the current classificatory problems in psychiatry were faced in general medicine and are 'susceptible to a similar solution'. The way forward advocated here is first to position depressive conditions at a domain level (whether brain diseases or as personality-based or situational in being precipitated by stressors) and then examine the extent to which clusters can be derived for later operational diagnoses. For those clusters that allow phenomenological definition to a sufficient degree, pursuit of underlying causes can then sharpen their clinical definition by repeatedly reworking the predictor and outcome variables. This is not merely a return to the past and the risk of undue weighting of phenomenology and descriptive psychiatry. This approach can be used as a template for melding phenomenological and aetiological data acquired by sophisticated research paradigms to form more precise 'fuzzy sets'.

The American science fiction writer Poul Anderson once observed that: 'I have yet to see any problem, however complicated, which, when you looked at in the right way, did not become more complicated.' The evidently low utility of the DSM and ICD systems (and constructs used within them such as 'major depression', 'dysthymia',and 'melancholia') leads to a challenge: to provide more fine-focused evidence demonstrating either that such diagnoses *do* inform us about differential causes and treatments or that alternatives such as the approach outlined here are more likely to lead to a diagnostic classification useful to clinicians and researchers.

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REFERENCES

Altschule, M. C. (1967) The two kinds of depression according to St Paul. *British Journal of Psychiatry*, **113**, 779–780.

American Psychiatric Association (1980) *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, Washington, DC: American Psychiatric Association.

American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Illness*, 3rd edition (revised) (DSM-III-R), Washington, DC: American Psychiatric Association.

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Washington, DC: American Psychiatric Association.

Bertelsen, A. (1999) Reflections on the clinical utility of the ICD-10 and DSM-IV classifications and their diagnostic criteria. *Australian and New Zealand Journal of Psychiatry*, **33**, 166–173.

Blashfield, R. K., and Morey, L. C. (1979) The classification of depression through cluster analysis. *Comprehensive Psychiatry*, **20**, 516–527.

Bryson, B. (2003) *A Short History of Nearly Everything*, Sydney, Australia: Doubleday.

Danish University Antidepressant Group (1986) Citalopram. Clinical effect profile and comparison with clomipramine: a controlled multicenter study. *Psychopharmacology*, **90**, 131–138.

Danish University Antidepressant Group (1990) Paroxetine. a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. *Journal of Affective Disorder*, **18**, 289–299.

Dilling, H. (2000) Classification, in M. G. Gelder, J. J. López-Ibor Jr and N. C. Andreasen (Eds), *New Oxford Textbook of Psychiatry*, pp. 109–133.

Goldney, R. D. (2006) The utility of the DSM nosology of mood disorders. *Canadian Journal of Psychiatry*, **51**, 874–877.

Grinker, R.R., Miller, J., Sabshin, M., *et al.* (1961) *The Phenomena of Depressions*, New York: Harper and Row.

Hickie, I. (1996) Issues in classification: III. Utilising behavioural constructs in melancholia research, in G. Parker and D. Hadzi-Pavlovic (Eds), *Melancholia: A Disorder of Movement and Mood. A Phenomenological and Neurobiological Review*, New York: Cambridge University Press, pp. 38–56.

Hickie, I., Parsonage, B., and Parker, G. (1990) Prediction of response to electroconvulsive therapy: preliminary validation of a sign-based typology of depression. *British Journal of Psychiatry*, **157**, 65–71.

Hiller, W., Dichtl, G., Hecht, H., *et al.* (1993). An empirical comparison of diagnoses and reliabilities in ICVD-10 and DSM-III-R. *European Archives of Psychiatry and Clinical Neuroscience*, **242**, 209–217.

Judd, L. L., Paulus, M. P., Wells, K. B., *et al.* (1996) Socioeconomic burden of subsyndromal depressive symptoms and major depression in a sample of the general population. *American Journal of Psychiatry*, **153**, 1411–1417.

Kendell, R. E. (1976) The classification of depressions: a review of contemporary confusion. *British Journal of Psychiatry*, **129**, 15–58.

Kendell, R. E. (1989) Clinical validity, in L. N. Robins and J. E. Barrett (Eds), *The Validity of Psychiatric Diagnosis*, New York: Raven Press, pp. 305–323.

Khan, A., Khan, S., and Brown, W. A. (2002) Are placebo controls necessary to test new antidepressants and anxiolytics? *International Journal of Neuropsychopharmacology*, **5**, 193–197.

Kiloh, L. G., Andrews, G., Neilson, M., *et al.* (1971) The relationship of the syndromes called endogenous and neurotic depression. *British Journal of Psychiatry*, **121**, 183–196.

Kirk, S. A., and Kutchins, H. (1992) *The Selling of DSM: The Rhetoric of Science in Psychiatry*, Hawthorne, New York: Aldine de Gruyter.

Mapother, E. (1926) Manic-depressive psychosis. *British Medical Journal*, **2**, 872–877.

Maudsley, H. (1895) *The Pathology of the Mind: A Study of its Distempers, Deformities and Disorders*, London and New York: Macmillan.

McHugh, P. R. (2005) Striving for coherence. Psychiatry's efforts over classification. *Journal of American Medical Association*, **293**, 2526–2528.

Nelson, J.C., and Charney, D. S. (1981) The symptoms of major depressive illness. *American Journal of Psychiatry*, **138**, 1–13.

Parker, G. (2002) Differential effectiveness of newer and older antidepressants appears mediated by an age effect on the phenotypic expression of depression. *Acta Psychiatrica Scandinavica*, **106**, 168–170.

Parker, G. (2004) Critique of the guidelines for the treatment of depression: flaws in the construction. *Australian and New Zealand Journal of Psychiatry*, **38**, 885–890.

Parker, G. (2005) Beyond major depression. *Psychology Medicine*, **35**, 467–474.

Parker, G. (2007a) Head to head. Is depression overdiagnosed? Yes. *British Medical Journal*, **335**, 328.

Parker, G. (2007b) Atypical depression: a valid subtype? *Journal of Clinical Psychiatry*, **68** (Suppl. 3), 18–22.

Parker, G. (2007c) Defining melancholia: the primacy of psychomotor disturbance. *Acta Psychiatrica Scandinavica*, **115** (Suppl. 433), 21–30.

Parker, G., and Crawford, J. (2007) A spectrum model for depressive conditions: extrapolation of the atypical depression prototype. *Journal of Affective Disorders*, **103**, 155–163.

Parker, G., and Hadzi-Pavlovic, D. (1996) *Melancholia: A Disorder of Movement and Mood. A Phenomenological and Neurobiological Review*, New York: Cambridge University Press.

Parker, G., and Manicavasagar, V. (2005) *Modelling and Managing the Depressive Disorders*, Cambridge, UK: Cambridge University Press.

Parker, G., Gladstone, G., Roussos, J., *et al.* (1998) Qualitative and quantitative analyses of a 'lock' and 'key' hypothesis of depression. *Psychology and Medicine*, **28**, 1263–1273.

Parker, G., Hadzi-Pavlovic, D., Hickie, I., *et al.* (1991) Psychotic depression: a review and clinical experience. *Australian and New Zealand Journal of Psychiatry*, **25**, 169–180.

Parker, G., Hadzi-Pavlovic, D., Wilhelm, K., *et al.* (1994) Defining melancholia: properties of a refined sign-based measure. *British Journal of Psychiatry*, **164**, 316–326.

Parker, G., Hickie, I., Hadzi-Pavlovic, D. (1996) Psychotic depression: clinical definition, status and the relevance of psychomotor disturbance to its definition, in G. Parker and D. Hadzi-Pavlovic (Eds), *Melancholia: A Disorder of Movement and Mood*, New York: Cambridge University Press, pp. 179–201.

Parker, G., Mitchell, P., Wilhelm, K., *et al.* (1999) Are the newer antidepressant drugs as effective as established physical treatments? Results from an Australasian clinical panel review. *Australian and New Zealand Journal of Psychiatry*, **33**, 874–881.

Parker, G., Roussos, J., Eyers, K., *et al.* (1997a) How distinct is 'distinct quality' of mood? *Psychology and Medicine*, **27**, 445–553.

Parker, G., Roussos, J., Mitchell, P., *et al.* (1997b) Distinguishing psychotic depression from melancholia. *Journal of Affective Disorders*, **42**, 155–167.

Parker, G., Roy, K., Hadzi-Pavlovic, D., *et al.* (1992) Psychotic (delusional) depression: a meta-analysis of physical treatments. *Journal of Affective Disorders*, **24**, 17–24.

Parker, G., Roy, K., Mitchell, P., *et al.* (2002) Atypical depression: a reappraisal. *American Journal of Psychiatry*, **159**, 1470–1479.

Parker, G., Roy, K., Wilhelm, K., *et al.* (2001) Assessing the comparative effectiveness of antidepressant therapies: a prospective clinical practice study. *Journal of Clinical Psychiatry*, **62**, 117–125.

Paykel, E. S. (1971) Classification of depressed patients: a cluster analysis derived grouping. *British Journal of Psychiatry*, **118**, 275–288.

Posternak, M. A., and Zimmerman, M. (2002) Partial validation of the atypical features subtype of major depressive disorder. *Archives of General Psychiatry*, **59**, 70–76.

Roth, M., and Barnes, T. R. E. (1981) The classification of affective disorders: A synthesis of old and new concepts. *Comprehensive Psychiatry*, **22**, 54–77.

Rush, A. J., and Weissenburger, J. E. (1994) Melancholic symptom features and DSM-IV. *American Journal of Psychiatry*, **151**, 489–498.

Sartorius, N., Kaelber, C. T., Cooper, J.E., *et al.* (1993) Progress toward achieving a common language in psychiatry. *Archives of General Psychiatry*, **50**, 115–124.

Spiker, D. G., Weiss, J. C., Dealy, R. S., *et al.* (1985) The pharmacological treatment of delusional depression. *American Journal of Psychiatry*, **142**, 430–435.

Taylor, M. A, and Fink, M. (2006) *Melancholia. The Diagnosis, Pathophysiology, and Treatment of Depressive Illness*, Cambridge, UK: Cambridge University Press.

World Health Organization (1992) *The ICD-10 Classification of Mental and Behavioural Disorders – Clinical Descriptions and Diagnostic Guidelines* (International Classification of Diseases, 10th revision), Geneva, Switzerland: World Health Organization.

Zimmerman, M., Black, D. W, and Coryell, W. (1989) Diagnostic criteria for melancholia. The comparative validity of DSM-III and DSM-III-R. *Archives of General Psychiatry*, **46**, 361–368.

COMMENTARY 1.1

Four Questions and an Alternative

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This commentary provides a comprehensive and scholarly review of the recent history of diagnostic schemas and conventions for depressive disorders and proposes a novel schema for DSM-V and ICD-11. Arguing that the diagnostic reliability of the present category of major depressive disorder is overrated and has 'failed to demonstrate any coherent pattern of neurobiological changes or treatment specificity', Parker points out that the melancholic, atypical and psychotic subtypes show the most promise to provide more biological or treatment homogeneity. However, he argues persuasively that the categories of melancholic and atypical depression, as presently defined by DSM-IV, lack adequate diagnostic precision and consistency of treatment outcome data to qualify as discrete subtypes. In the case of melancholic depression, Parker postulates that the problem with diagnostic specificity has been reliance on symptom patterns for classification and provides data to support observable psychomotor disturbance as the specific and discriminating feature of the melancholic subtype. One problem with this new definition, however, is that calling upon the myriad of previous treatments and other psychobiologic studies to help validate this 'new' subtype may not be possible. Most previous studies used criteria to define melancholia (or the nearly synonymous terms, endogenous, autonomous, endogenomorphic, etc.) that did not require psychomotor changes for the diagnosis, may or may not have used clinical observations to identify whether agitation or retardation were present and almost never used objective measures to define threshold psychomotor changes. Perhaps it would reduce confusion to rename this category 'psychomotor disturbance depressive disorder'.

In Parker's model, nonmelancholic depression, composed of individuals with neurotic characterologic styles and stress-induced disorders, is too heterogeneous and nondistinct to warrant the status of a categorical class. Parker's proposed nosology harkens back to the pre-DSM-III dichotomy of neurotic/reactive depression versus melancholic/endogenous/psychotic depression. As in the older debate, the former group is characterised as less biological, more reactive and responsive to environmental events and psychosocial treatments, and less responsive to antidepressant medications or ECT. Furthermore, the melancholic depressions can be divided into those with and without psychosis.

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In addition, Parker theorises that nonmelancholic depressions are related to serotonin neurotransmission, melancholic depressions to serotonin plus norepinephrine neurotransmission and psychotic depression to serotonin, norepinephrine and dopamine neurotransmission. While there is much to say for Parker's carefully thought-out arguments, the classification of depressive disorder remains challenging and the last chapter has not yet been written. At least four unresolved issues remain:

1. *Is psychotic depression ready to be classified as a distinct subtype of depressive disorders?*

   Attempts to validate 'psychotic depression' have not been entirely consistent (Schatzberg and Rothscild, 1992), with several recent studies raising questions about the unique pattern of treatment response for psychotic depression (Zanardi *et al.*, 2000; Wijkstra *et al.*, 2006) and one comprehensive review (Keller, Schatzberg and Maj, 2007) finding only partial support for such a distinct subtype based on clinical symptoms, clinical course, familial history, cognitive symptoms, biological features and treatment response. Furthermore, boundaries between depression with psychotic features and bipolar depressions remain a clinical quagmire.
2. *Is melancholic depression ready to be classified as a distinct subtype of depressive disorders?*

   On the basis of inconsistent data on psychobiological validators of 'melancholic depression', Rush and Weissenburger (1994) recommended retaining melancholic features as one of the DSM-IV depression specifiers and noted that further research to test their distinct biological and psychological features was necessary. In the intervening years no consistent picture has yet emerged (Greenberg *et al.*, 2008; Fink *et al.*, 2007). In addition, as with psychotic depression, the boundaries between melancholia depressions, mixed states and bipolar disorder need clarification (Benazzi, 2002; Akiskal and Akiskal, 2007).
3. *Is major depressive disorder a term that has outlived its usefulness?*

   While it is clear that nosology is ideally based on specific aetiologic mechanisms and established pathophysiology (Insel and Scolnick, 2006), we are not there yet and must do the best we can within the constraints of our current knowledge. The category of major depressive disorder, as presently defined, does provide useful information to clinicians, epidemiologists and researchers. It is a common disorder, resulting in considerable role impairment, disability, medical morbidity, mortality and suicide risk (Rush, 2007). Although treatment is imperfect, the syndrome of major depressive disorder is at least somewhat responsive to antidepressant medications and specific forms of psychotherapy (Wolf and Hopko, 2008).
4. *Is there a viable alternative model to the one presented by Parker?*

   Several investigators have argued the advantages of adding a significant dimensional component to complement the categorical dimensions of depressive disorders (Reiger, 2007; Helzer, Kraemer and Krueger, 2006). Depressive disorders are essentially dimensional in nature, with a full breadth of affective symptomatology, including periods of syndromal depression alternating with other periods of subthreshold depression and even euthymia in the same patient over time (Judd *et al.*, 1998). Numerous studies have documented the importance of subthreshold symptoms, as they are associated with distress, impairment, increased health care utilisation and risk of suicide. Even one residual depressive symptom can increase risk for recurrence (Judd *et al.*, 2000). Thus,

categories of psychopathology may be seen as arbitrary and fail to capture much important information regarding boundaries with normal behaviour, subthreshold symptoms and syndromes and other categories. Dimensional diagnoses have the advantage of more fully describing and delineating depressive disorders, reducing co-morbidity, allowing symptom weighing, introducing noncriteria symptoms, reducing 'not otherwise specified' (NOS) categories and providing more specific direction to clinicians and biological researchers (Andrews *et al.*, 2007). Thus, the leaders of DSM-V and ICD-11 have championed the incorporation of dimensional approaches to refine the diagnosis of all major psychiatric disorders, including depression (Reiger, 2007). Much of the discussion is focused on which dimensions, how many and how they should be measured. Dimensional assessments to characterise depressed patients might include all the symptoms presently comprising the diagnosis of major depressive disorder and its subtypes; associated noncriteria symptoms such as suicidality, anxiety, somatic pain, irritability/anger and mood lability; severity; recurrence; psychotic symptoms; substance use; age of onset; duration of present episode; cycling; and features of functioning and quality of life. Within the broad category, it will still be possible to retain the DSM-IV and ICD-10 diagnosis of major depressive disorder, although different symptomatic, duration or impairment cutoffs for specific treatment strategies, epidemiological studies or research purposes may prove desirable. Such a diagnostic system will facilitate further assessment of the usefulness, boundaries and validity of specific proposed categories of depression, including 'melancholic' and 'psychotic' subtypes.

REFERENCES

Akiskal, H.S., and Akiskal, K. K. (2007) A mixed state core for melancholia: an exploration in history, art and clinical science. *Acta Psychiatrica Scandinavica* (Suppl.), **433**, 44–49.

Andrews, G., Slade, T., Sunderland, M., *et al*. (2007) Issues for DSM-V: simplifying DSM-IV to enhance utility: the case of major depressive disorder. *American Journal of Psychiatry*, **164**(12), 1784–1785.

Benazzi, F. (2002) Bipolar depression and melancholia. Comments on Parker et al., 'The nature of bipolar depression: implications for the definition of melancholia'. *Journal of Affective Disorder*, **72**(2), 201–202.

Fink, M., Rush, A. J., Knapp, R., *et al*. (2007) Consortium for Research in ECT (CORE) Study Group. DSM melancholic features are unreliable predictors of ECT response: A CORE Publication. *Journal of ECT*, **23**(3), 139–146.

Greenberg, D. L., Payne, M. E., MacFall, J. R., *et al*. (2008) Hippocampal volumes and depression subtypes. *Psychiatry Research*, **163**(2), 126–132.

Helzer, J. E., Kraemer, H. C., and Krueger, R. F. (2006) The feasibility and need for dimensional psychiatric diagnoses. *Psychology in Medicine*, **36**(12), 1671–1680.

Insel, T. R., and Scolnick, E. M. (2006) Cure therapeutics and strategic prevention: raising the bar for mental health research. *Molecular Psychiatry*, **11**(1), 11–17.

Judd, L. L., Akiskal, H. S., Maser, J. D., *et al*. (1998) A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. *Archives of General Psychiatry*, **55**(8), 694–700.

Judd, L. L., Paulus, M., Schettler, P., *et al.* (2000). Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? *American Journal of Psychiatry*, **157**, 1501–1504.

Keller, J., Schatzberg, A. F., and Maj, M. (2007) Current issues in the classification of psychotic major depression. *Schizophrenia Bulletin*, **33**(4), 877–885.

Reiger, D. (2007) Dimensional approaches to psychiatric classification: refining the research agenda for DSM-V: an introduction. *International Journal of Methods in Psychiatric Research*, **16**(Suppl. 1), S1–5.

Rush, A. J. (2007) The varied clinical presentations of major depressive disorder. *Journal of Clinical Psychiatry*, **68**(Suppl. 8), 4–10.

Rush, A. J., and Weissenburger, J.E. (1994) Melancholic symptom features and DSM-IV. *American Journal of Psychiatry*, **151**(4), 489–498.

Schatzberg, A. F., and Rothschild, A. J. (1992) Psychotic (delusional) major depression: should it be included as a distinct syndrome in DSM-IV? *American Journal of Psychiatry*, **149**, 733–745.

Wijkstra, J., Lijmer, J., Balk, F. J., *et al*. (2006) Pharmacological treatment for unipolar psychotic depression: systematic review and meta-analysis. *British Journal Psychiatry*, **188**, 410–415.

Wolf, N. J., and Hopko, D. R. (2008) Psychosocial and pharmacological interventions for depressed adults in primary care: a critical review. *Clinical Psychology Review*, **28**(1), 131–161.

Zanardi, R., Franchini, L., Serretti, A., *et al*. (2000) Venlafaxine versus fluvoxamine in the treatment of delusional depression: a pilot double-blind controlled study. *Journal of Clinical Psychiatry*, **61**(1), 26–29.

COMMENTARY 1.2

The Blurring of Caseness in Depressive Disorders

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Ancient Egyptians recognised depression 6000 years ago as a unitary dimension attributed to heart ailments in Eber's papyrus. Depression was treated as a heart disease and its description of psychomotor disturbance, lower self-esteem and death wishes were explained. Because of its attribution to heart disease, there was no stigma around depression or mental disorders (Okasha and Okasha, 2000).

The chapter by Gordon Parker is a thought-provoking debate regarding the current classification of depressive disorders. It seems we are back to square one from 50 years ago, nostalgic about endogenous and reactive depression or unitary or binary systems. We are still in disharmony regarding separating unipolar and bipolar types, especially after scientific evidence that bipolar disorder and schizophrenia have more similarity than dissimilarity. Parker quotes Altschule (1967), pointing out that in the *Bible* St Paul refers to two types of depression: one 'from God' (inexplicable or endogenous) and the other 'of the world' (i.e. exogenous or reactive).

An important issue raised by Parker is the problem of caseness and the overdiagnosis of depression. Our present classificatory systems, DSM-IV and ICD-10, do not have a sharp boundary between normal existential mood of depression and pathological depression. At the same time, there is blurring of depressed affect, depressed mood and pathological depression.

The combinations of variables for depression lead to more than 200 diagnoses in DSM-IV (American Psychiatric Association, 1980). The system is almost dimensional, based on severity, persistence and recurrence, and semi-categorical in psychotic, melancholic and atypical depression. In ICD-10 (World Health Organization, 1992) there is a unitarian dimensional system across severity, persistence and recurrence, with more than 100 categories to which a depressed patient can be assigned.

Once our diagnosis is atheoretical and depends on a cluster of symptoms and signs that are rather subjective, how a person is diagnosed may depend to a great extent on how

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mental symptoms are perceived. For example, in traditional religious societies withdrawal, psychomotor retardation and overindulgence in religious duties may be signs of piousness, nearness to God and contemplation on the day of judgement. Some of the depressive symptoms are perceived as traits that are cherished by the society and the person will be looked at as a blessed person rather than depressed. It will be violation of the social codes if a psychiatrist gives the person a medical diagnosis. Some may claim that psychiatrists are attempting to medicalise religiosity because they are secular and friends of Satan. The same applies for negative symptoms, which always have religious connotations. Even personality disorders may be viewed differently: an avoidant displays a desired religious politeness and timidity; a paranoid is a careful person; the schizoid is a kind, passionate person contemplating about God, against the infidel and apostates; the obsessive is a person adhering to and complying with his religious duties, especially as obsessions in depression are usually associated with blasphemous thoughts and attributed to the Satan in these cultures (Okasha, 2001).

These cultural factors may influence the prevalence and diagnosis of depression. In the 1950s, for example, Carothers explained the African mind as being unable to suffer from depression. This proved to be completely wrong. Psychiatric disorders in general, and depressive disorders in particular, are the outcome of the interaction of biopsychosocial factors. Ethnicity, culture and socioeconomic factors all contribute to the prevalence, causation, clinical presentation and outcome of depression.

Difficulties in using the lexicon describing emotions are also universal. For example, difficulties were encountered in translating the words 'anxiety' and 'depression' to Yoruba language. Leighton and his colleagues had to use phrases like 'the heart is weak' and 'the heart is not at rest' in their translation. No words could be found to stand for anxiety, tension and worrying in the Chinese language (Leff, 1986; Leighton *et al.*, 1963).

Native and layperson's language rather than clinical professional lexicon may be closer to the subject's perceived emotions. El-Assra (1989) observed, for example, that a good proportion of Saudi patients usher their complaint by referring to 'deega'. Analysis of this term in his study revealed that it has psychological, cognitive and somatic connotations. Basically, it conveys the sense of chest oppression or tightness. In colloquial Saudi Arabic it means an uncomfortable and unpleasant feeling of unhappiness and fear with a sense of narrowness. Translated instruments carry the risk of reductionism of these phenomena and alienation from actual experience (Rakhawy, 1987).

Another issue regarding current diagnostic systems is raised by Karam and colleagues (Karam, 1994; Karam *et al.*, 1998). In a community survey, they estimated the one-year prevalence of major depressive disorders to be 34 %, of which 6 % could be attributed to the effects of bereavement. Depressive and post-traumatic stress disorders were both linked and the risk was augmented during the more traumatic and bloody stages of war. Karam *et al.* argue convincingly that the characteristics of bereavement depression do not differ from any other major depression and therefore should not be specifically excluded from the DSM-IV classification of that disorder (Karam, 1994; Karram *et al.*, 1998).

Parker and Crawford's (2007) attempts to delineate psychotic depression, melancholic depression and nonmelancholic depression is worthy of scrutiny, leaving the dimensional system for severity (where subthreshold depression can be accommodated), persistence and recurrence. The multiple ICD-10 and DSM-IV depressive categories merge into one another and the boundaries between them are – in several cases – explicitly arbitrary. Nor do we have evidence of boundaries or 'points of rarity' (Kendell and Brockington, 1980)

between the depressive syndrome (ICD-10's depressive episode or DSM-IV's major depression) and either normal sadness or the symptoms of bereavement; between depressions and anxiety states; or between psychotic depressions and schizophrenia. As recent large-scale population-based surveys have shown, whatever putative boundary one examines, the variation in symptomatology is continuous, and so far neither discriminant functions, twin and family studies, neuroendocrine tests nor neuroimaging have come to our rescue. It is likely, too, that we will be unable to develop a classification of depressive disorders that is demonstrably superior to our present classifications until we have identified the genes involved and are beginning to understand how their products interact with the various environmental risk factors (Kendell, 2001).

A study on a community sample by Parker in 2007 showed that 89 % met criteria for wide definitions of depression by their late thirties. This is alarming news that our current diagnosis encompasses all depressed affect, moods and existential mood swings and blurs the distinction between normality and caseness.

We need a simpler, more objective, culture- and religion-sensitive classification that differentiates pathological depression 'from God' and nonmelancholic depression from stressful events.

REFERENCES

Altschule, M. C. (1967) The two kinds of depression according to St Paul. *British Journal of Psychiatry*, **113**, 779–780.

American Psychiatric Association (1980) *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, Washington, DC: American Psychiatric Association.

El-Assra, A. (1989) The complaint of 'tightness' in the Saudi population. Paper read at the VIIIth World Congress on Psychiatry, Athens, Greece.

Karam, E. G. (1994) The nosological status of bereavement-related depressions. *British Journal of Psychiatry*, **165**, 48–52.

Karam, E. G., Howard, D., Shaaya, M., *et al*. (1998) Les guerres du Liban: Comorbidite de la depression et troubles post-traumatiques. *Journal Clinique et Biologique*, **3**, 14–17.

Kendell, R. E. (2001) Much diversity, many categories, no entities, in M. E. Medina-Mora and N. Sartorius (Eds), *Depressive Disorders*, Chichester: John Wiley & Sons, Ltd.

Kendell, R. E., and Brockington, I. F. (1980) The identification of disease entities and the relationship between schizophrenic and affective psychoses. *British Journal of Psychiatry*, **137**, 324–331.

Leff, J. P. (1986) The epidemiology of mental illness across cultures, in John L. Cox (Ed.), *Transcultural Psychiatry*, London: Croom Helm.

Leighton, A. H., Lambo, T. A., Hughes, C. C., *et al*. (1963) *Psychiatric Disorder among Yoruba*, New York: Cornell University Press.

Okasha, A. (2001) OCD: a transcultural approach from an Egyptian Islamic perspective, in A. Okasha and M. Maj (Eds), *Images in Psychiatry; 'An Arab Perspective'*, Cairo, Egypt: World Psychiatric Association, Scientific Book House.

Okasha, A. and Okasha, T. (2000) Notes on mental disorders in Pharaonic Egypt. *History of Psychiatry*, **xi**, 413–424.

Parker, G. (2007) Head to head. Is depression overdiagnosed? Yes. *British Medical Journal*, **335**, 328.

Parker, G., and Crawford, J. (2007) A spectrum model for depressive conditions: extrapolation of the atypical depression prototype. *Journal of Affective Disorders*, **103**, 155–163.

Rakhawy, Y. T. (1987) Psychic phenomena in the hazards of translation. *Egyptian Journal of Psychiatry*, **10**, 9–10.

World Health Organization (1992) *The ICD-10 Classification of Mental and Behavioural Disorders – Clinical Descriptions and Diagnostic Guidelines*, Geneva, Switzerland: World Health Organization.

COMMENTARY 1.3

Fresh Look at Alternatives for Diagnosing Depression

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The difficulties in diagnosing and classifying depressive disorders have become as much of a charm as understanding and treating them (if one considers challenges as charms)! It is difficult to speculate how the problems in classifying depression will resolve, given the heterogeneity and complexity of its presentation. The different issues pertaining to diagnosing and classifying depressive disorders have been critically evaluated and lucidly discussed by Gordon Parker, as by many other authors over the last half a century. A few other issues need attention.

The criteria-based diagnosis has its advantages, especially for clinical drug trials, but poses challenges in clinical practice. Many symptoms of depression, the way these present or their qualitative alteration have been considered to be morbid or pathological. However, are all symptoms *equally* morbid or pathological? For example, is there equity between psychomotor disturbance, loss of appetite and suicidal thoughts or attempts; or between sadness of mood and anhedonia; or between diurnal variation of mood and early morning awakening; or between the numerous depressive cognitions. Some symptoms reduce quality of life (sadness, anhedonia, psychomotor retardation), some produce distress (anxiety, sadness, insomnia, depressive thoughts) and some are potentially life threatening (suicidal thoughts, attempts, loss of weight). Have such comparisons been addressed in a research design? This is a drawback of the current classificatory systems, which depend on counting the number of symptoms present in order to make a diagnosis. This system presumes that all the symptoms are of equal importance and morbidity. The problems in diagnosing and treating depressive disorders when the number of symptoms is insufficient are well recognised. The distress in subthreshold depressive disorders has been discussed in the literature and the need for its treatment has been acknowledged. Counting numbers of symptoms or measuring scores on depression scales appears futile.

Similarly, the duration criteria have their limitations. If a person identifies severe symptoms for a few hours or a day or two, can it not be diagnosed as a depressive disorder? This is particularly true of a person who has had previous episodes of depression and may perceive a relapse early enough.

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In this chapter, Gordon Parker has rightly suggested a need for examining alternative models for classifying depressive disorders. One such model could be a multiaxial system that also incorporates aetiological factors. Other axes could be related to duration, severity, presence or absence of main classes of symptoms. For example, the signs and symptoms of depression can be classified into certain categories – mood symptoms, behavioural symptoms, cognitive symptoms, biological symptoms, physical symptoms and psychotic symptoms. Specifying these categories in the multiaxial diagnosis may appear cumbersome and lengthy; however, this would encourage further research into the biological mechanisms that underlie these categories. There may be a justification to reconsider aetiology in the diagnosis as it would have implications for management.

The terminology of depressive disorders and related specifiers has created confusion across the globe. The use of 'somatic symptoms' is one such example; it indicates vegetative symptoms in certain parts of the world and denotes physical symptoms in other parts. Whereas the DSM-IV includes changes in appetite and weight, sleep disturbances, lack of concentration and diminished ability to think or indecisiveness as somatic symptoms of depression, most clinicians and patients talk about headache, body ache, fatigue, tiredness, bodily sensations and other sensory changes as somatic symptoms. Melancholic features or vegetative features like diurnal variation, early awakening and retardation are also referred to as somatic symptoms when subclassifying major depressive disorder as one with 'somatic symptoms'.

The term 'depressive disorder' itself is no less depressing. The alternatives for this nomenclature – 'mood disorder' or 'affective disorder' – are no better to be adequately and properly understood by the general public or professionals. The revival and resurgence of the term 'melancholia' does not help matters much; similarly the connotation of 'bipolar' could be misleading. Diagnosing depression as major or minor depression, masked and double depression is confusing to those who are fresh trainees into psychiatry. The implications could be misleading, as chronic minor depression may be more distressing than brief mild major depression. There are also difficulties in diagnosing the erstwhile atypical depression and neurotic depression. This assumes importance since in clinical practice one still encounters these categories. One should search for an appropriate scientific and medical term to describe depressive disorders. Currently, a web search for 'depression' leads to depression in the stock market, weather, earth, endocrinal functions, depressed fractures and bones, to name a few. The term 'depression' is too general and vague, and it is time for it to be replaced in the psychiatric nomenclature and taxonomy.

Overall, there are more problems and difficulties diagnosing and classifying depressive disorders than solutions. Many attempts are being made to reduce the difficulties, but no appropriate solution seems to be emerging in the horizon.

COMMENTARY 1.4

Severity and Subtypes of Depression

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Every creative new suggestion for defining subgroups of depression is welcome, especially a new definition of melancholia, as given by Gordon Parker, based on precise measures of psychomotor activity. The main point of the author goes further, however, as he proposes a new classification of depressive disorders.

DIMENSIONAL CONCEPT OF DEPRESSION

The current concept of depression is mainly categorical but also takes account of *severity*. On the diagnostic level, DSM-IV distinguishes between categorical subgroups: psychotic major depression, nonpsychotic major depression, dysthymia and minor depression and so on, which together are considered to form a *spectrum* of diagnoses. ICD-10 distinguishes mild, moderate and severe depression on the basis of severity. It is widely agreed that we need a combined categorical and dimensional approach for the diagnosis and classification of depression. The categorical approach is necessary for clinical practice and the dimensional one is important for clinical and biological research, e.g. for research into the long-term course of the disorder (Judd, no date; Judd *et al.*, 1998) or in the field of molecular genetics (Craddock *et al.*, 2007).

We all know from personal experience what our basic emotions are – anxiety, depression, anger/irritability and elation (Zinck and Newen, 2007) – and how our emotions and mood continuously fluctuate. The demarcation line to a disorder is a fluid one too, and depends on many factors. There is no way out of the dilemma that we have to define 'what is a case' (Wing, Bebbington and Robbins, 1981) on this severity dimension. Such a definition can vary over the years, reflecting scientific progress and specific purpose; a physiological analogy is to be found in the definition of pathological blood pressure, which has undergone constant redefinition over the years.

Unfortunately, the severity 'measures' in psychiatry are not very precise; they usually consist of estimates referring to the past (number of symptoms, days spent with symptoms

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over one/two years, episode duration and frequency, distress, impairment in social roles – work, relationships, leisure). Certain symptoms also reflect severity directly (delusions, hallucinations). Interestingly, Gordon Parker's proposals, based partially on McHugh (2005), to distinguish four types of depression – psychotic depression, melancholic depression, nonmelancholic depression (former neurotic depression) and nonmelancholic depression induced by stress (former reactive depression) – can also be projected on to a severity dimension. An order of severity is also inherent in the three-type solution: psychotic, melancholic and nonmelancholic.

TREATMENT STUDIES

For certain comparisons (e.g. testing the validity of a new diagnostic group) it is necessary to stratify by the total number of the criterial symptoms of major depressive episode. This is especially true for comparisons, for instance, between melancholic and nonmelancholic depression. In treatment trials baseline severity must be comparable. Gordon Parker is right that it is very difficult to prove diagnostic utility by randomised placebo-controlled trials of antidepressants, because they usually exclude severely depressed and suicidal cases and refer to mildly or moderately depressed patients on whom the effects of various strength antidepressants or psychotherapy may be the same and hard to distinguish from placebo. He is also right in stating that treatment trials have shown that in severe depression there can be marked differences between treatment subtypes, for instance between SSRIs and TCAs (Danish University Antidepressant Group, 1990). An increasing baseline severity of depression correlates with decreasing response rates to placebo and with rising response rates to TCAs and moclobemide (Angst, 1993, 1995). So the baseline severity of depression is extremely important and must also be controlled in trials that compare melancholic and nonmelancholic depressives, as reported by Parker (2002). The nonspecific results of RCTs in milder depressives cannot be generalised as Parker does in his interpretation that 'a non-specific diagnosis must be expected to risk non-specific results in relation to . . . treatment differentiation'.

AETIOLOGY

It would certainly be desirable to classify depression by aetiology as suggested by Gordon Parker. For the time being, however, this seems to be premature, since all we know is that the aetiology is multifactorial, including multiple genetic, epigenetic and environmental elements. Until we are wiser, it is advisable to apply descriptive dimensional measures as much as possible. The same is true for specific subtypes like melancholic or atypical depression. The redefinition of melancholia by observable psychomotor disturbance as proposed by Parker is important and should stimulate further research.

REFERENCES

Angst, J. (1993) Severity of depression and benzodiazepine co-medication in relationship to efficacy of antidepressants in acute trials. A meta-analysis of moclobemide trials. *Human Psychopharmacology*, **8**, 401–407.

Angst, J. (1995) The efficacy of moclobemide (1977–1994). A meta-analysis, in *Farmakoterapia w Psychiatrii I Neurologii*: I-MAO, RIMA w Leczeniu depresji, pp. 31–48.

Craddock, N., O'Donovan, M. C., and Owen, M. J. (2007) Phenotypic and genetic complexity of psychosis. *British Journal of Psychiatry*, **190**, 200–203.

Danish University Antidepressant Group (1990) Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. *Journal of Affective Disorders*, **18**, 289–299.

Judd, L. L. (no date) Gilman Marston M. Stecker monograph. Major depressive disorder (MDD): a new paradigm.

Judd, L. L., Akiskal, H. S., Maser, J. D., *et al.* (1998) A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. *Archives of General Psychiatry*, **55**, 694–700.

McHugh, P. R. (2005) Striving for coherence. Psychiatry's efforts over classification. *Journal of American Medical Association*, **293**, 2526–2528.

Parker, G. (2002) Differential effectiveness of newer and older antidepressants appears mediated by an age effect on the phenotypic expression of depression. *Acta Psychiatrica Scandinavica*, **106**, 168–170.

Wing, J. K., Bebbington, P., and Robins, L. N. (1981) *What Is a Case? The Problem of Definition in Psychiatric Community Surveys*. London: Grant McIntyre.

Zinck, A., and Newen, A. (2008) Classifying emotion: a developmental account. *Synthese*, **161**, 1–25.

COMMENTARY 1.5

Severe Depression and Melancholia

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Professor Parker has developed a number of points made quite timely by the revisions of the DSM now underway. Of the areas most in need of attention, one has roots in the early adoption of a unitary rather than a binary concept for major depressive disorder and the low threshold for caseness thought necessary to encompass a full severity spectrum. The result has been a disorder that, in seeming contradiction to the term 'major', is often forgettable. The Collaborative Depression Study illustrated this when it re-interviewed the relatives, controls and spouses of probands six years after their initial evaluation. Of 171 relatives who had described a lifetime history of at least one episode of major depressive disorder when initially evaluated, only 65 % recalled having had any episode when re-interviewed (Rice *et al.*, 1987). Nearly all of the characteristics that significantly separated the remembered from the forgotten episodes – episode duration, number of symptoms, degree of impairment, treatment seeking – reflected severity.

The major depressive disorder episodes that nearly 23 % of the relatives, controls and spouses developed in the six-year interval (Coryell, Endicott and Keller, 1992) indicated a problematically high lifetime prevalence. A younger age was strongly associated with the probability of a major depressive disorder onset (Coryell, Endicott and Keller, 1992) so that, when observed risks for onset in each age decade were considered, 100 % of subjects in their twenties and thirties were projected to have a lifetime history of major depressive disorder by age 70 (Coryell, unpublished data). Second, though two in five of those who experienced a major depressive disorder episode failed to receive either psychotherapy or somatotherapy, this hardly indicated inadequacies in recognition or treatment availability because their mean time-to-remission was substantially shorter than that for individuals who did receive treatment (Coryell *et al.*, 1994). These findings underscore Professor Parker's point that, when steps are taken to correct for the forgetting of past episodes, the apparent lifetime prevalence of major depressive disorder in the community calls into question its status as a 'clinical' entity.

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These considerations, and the likelihood that DSM-V will retain a unitary approach, make it important that one or more subtype definitions are available that (1) reduce biological heterogeneity within that subgroup and thus facilitate research of all sorts; (2) identify individuals who are unlikely to respond to placebo or remit spontaneously, and thus aid the identification of effective new treatments; and (3) have relevance to the selection of existing treatment modalities.

The subcategory of psychotic major depressive disorder achieves all three of these goals and, while some clarifications and refinements are warranted, its definition is relatively straightforward. Among the other specifiers, 'with melancholic features' has the longest pedigree but its value, as currently defined, is debatable. Does it add anything useful to globally rated severity? Meta-analyses, for instance, have shown robust relationships between severity, as measured by the Hamilton Rating Scale for Depression, and the size of antidepressant–placebo differences in controlled treatment trials (Khan *et al.*, 2002). A number of studies have shown placebo response to be significantly less likely in depressed patients meeting criteria for melancholia (Heileigenstein, Tolefson and Faries, 1994; Peselow *et al.*, 1992; Davidson *et al.*, 1988; Fairchild *et al.*, 1986). In some (Heileigenstein, Tolefson and Faries, 1994; Peselow *et al.*, 1992), the distinction appeared a better predictor than severity in that groups did not differ by severity. There were, however, no efforts to determine how much the melancholic distinction added to overall severity in placebo response prediction.

Efforts to validate melancholia with biological measures, most notably the dexamethasone suppression test (DST), have likewise not controlled well for severity, though one did show a clearly discontinuous relationship between the number of endogenous (melancholic) symptoms present in an individual and the likelihood of DST nonsuppression (Zimmerman *et al.*, 1987).

Finally, an analysis of twin data showed a high concordance between melancholia and major depressive disorder in monozygous pairs but not between melancholia and melancholia (Kendler, 1997). This lack of subtype specificity led to the conclusion that the melancholia designation added little beyond indicating a more severe and thus more heritable condition.

Does the failure of melancholia to clearly rise above global severity as a predictor of placebo response, of heritability or of HPA-axis hyperactivity indicate the concept's inherent lack of validity or does it result, instead, from the inadequacies of the definitions that have been applied? The movement to devise and use fully operational criteria for psychiatric diagnoses was accompanied by an overriding concern for interrater reliability. This led to a preference for the phenomenological features traditionally associated with melancholia over the more subjective judgements concerning course of illness, personality and reactivity. Yet, though more difficult to define in ways that can be reliably applied, the exclusion of these components may have undermined the validity of the resulting definition. Indeed, patients with melancholia defined purely by symptoms appear less likely to have had recent adverse life events (Roy *et al.*, 1985; Zimmerman *et al.*, 1985b) or to have a personality disorder (Black *et al.*, 1988; Charney, Nelson and Quinlan, 1981), normal DST results (Roy, 1988; Zimmerman *et al.*, 1985a) or a placebo response (Brown *et al.*, 1992). In turn, the presence of a personality disorder in patients with major depressive disorder (Schweitzer *et al.*, 2001; Zimmerman, Coryell and Pfohl, 1986; Pfohl, Stangl and Zimmerman, 1984) and of recent adverse life events (Roy, 1988) have been associated with normal DST results.

Professor Parker and colleagues at the Black Dog Institute have accumulated a substantial body of research demonstrating that, when rigorously assessed, psychomotor disturbance, either retardation or agitation, comprises the most important component of the melancholic syndrome and that when the presence of melancholia is based on these features it is indeed associated with the qualities intended for melancholia. They have also shown that certain other components of current melancholia definitions should be omitted and still others emphasised or added. The time is now at hand to use these findings to derive criteria for melancholia that will comprise a truly useful and widely applied clinical tool.

REFERENCES

Black, D. W., Bell, S., Hulbert, J., *et al.* (1988) The importance of axis II in patients with major depression. *Journal of Affective Disorders*, **14**, 15–22.

Brown, W. A., Johnson, M. F., Chen, M. G., *et al.* (1992) Clinical features of depressed patients who do and do not improve with placebo. *Psychiatry Research*, **41**, 203–214.

Charney, D. S., Nelson, J. C., Quinlan, D. M. (1981) Personality traits and disorder in depression. *American Journal of Psychiatry*, **138**, 1601–1604.

Coryell, W., Endicott, J., and Keller, M. (1992) Major depression in a nonclinical sample. Demographic and clinical risk factors for first onset. *Archives of General Psychiatry*, **49**, 117–125.

Coryell, W., Akiskal, H. S., Leon, A. C., *et al.* (1994) The time course of nonchronic major depressive disorder. Uniformity across episodes and samples. *Archives of General Psychiatry*, **51**(5), 405–410.

Davidson, J. E. G, Zisook, S., *et al.* (1988) An efficacy study of isocarboxazide and placebo in depression, and its relationship to depressive nosology. *Archives of General Psychiatry*, **45**, 120–127.

Fairchild, C. J., Rush, A. J., Vasavada, N., *et al.* (1986) Which depressions respond to placebo? *Psychiatry Research*, **18**, 217–226.

Heileigenstein, J. H., Tolefson, G. D., Faries, D. E. (1994) Response patterns of depressed outpatients with and without melancholia: a double-blind, placebo controlled trial of fluoxetine versus placebo. *Journal of Affective Disorders*, **30**, 163–173.

Kendler, K. S. (1997) The diagnostic validity of melancholic major depression in a population based sample of female twins. *Archives of General Psychiatry*, **54**, 299–304.

Khan, A., Leventhal, R. M., Khan, S. R., *et al.* (2002) Severity of depression and response to antidepressants and placebo: an analysis of the Food and Drug Administration database [see comment]. *Journal of Clinical Psychopharmacology*, **22**, 40–45.

Peselow, E. D., Sanfilipo, M. P., Difiglia, C., *et al.* (1992) Melancholic/endogenous depression and response to somatic treatment and placebo. *American Journal of Psychiatry*, **149**, 1324–1334.

Pfohl, B., Stangl, D., Zimmerman, M. (1984) The implications of DSM-III personality disorders for patients with major depression. *Journal of Affective Disorders*, **7**, 309–318.

Rice, J. P., Endicott, J., Knesevich, M.A., *et al.* (1987) The estimation of diagnostic sensitivity using stability data: an application to major depressive disorder. *Journal of Psychiatric Research*, **21**, 337–345.

Roy, A. (1988) Cortisol nonsuppression in depression: relationship to clinical variables. *Journal of Affective Disorders*, **14**, 265–270.

Roy, A., Breier, A., Doran, A. R., *et al.* (1985) Life events in depression. Relationship to subtypes. *Journal of Affective Disorders*, **9**, 143–148.

Schweitzer, I., Tuckwell, V., Maguire, K., *et al.* (2001) Personality pathology, depression and HPA axis functioning. *Human Psychopharmacology and Clinical Experience*, **16**, 303–308.

Zimmerman, M., Coryell, W., Pfohl, B., *et al.* (1985a) Four definitions of endogenous depression and the dexamethasone suppression test. *Journal of Affective Disorders*, **8**, 37–45.

Zimmerman, M., Pfohl, B., Stangl, D., *et al.* (1985b) The validity of DSM-III axis IV (severity of psychosocial stressors). *American Journal of Psychiatry*, **142**, 1437–1441.

Zimmerman, M., Coryell, W., Pfohl, B. (1986) The validity of the dexamethasone suppression test as a marker for endogenous depression. *Archives of General Psychiatry*, **43**, 347–355.

Zimmerman, M., Coryell, W., Pfohl, B., *et al.* (1987) An American validation study of the Newcastle Diagnostic Scale. II. Relationship with clinical, demographic, familial and psychosocial features. *British Journal of Psychiatry*, **150**, 526–532.

COMMENTARY 1.6

The Need To Functionalise Psychiatric Diagnosis

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In commenting on Parker's scholarly and informative paper I restrict myself to a few points.

MAJOR DEPRESSION IS A CATEGORICAL CONSTRUCT

Parker calls the DSM-III based classificatory system 'a primarily dimensional model'. I question that qualification. Take major depression as an example. That diagnosis is based on a particular (but variable) set of symptoms, with a particular (but variable) duration, severity and course. Each of those parameters could have been used and expressed dimensionally, but they are not. They are instead lumped together in a diagnostic 'package', named major depression. In essence, major depression is a pure categorical construct, as is the case with most DSM-based diagnoses.

MAJOR DEPRESSION IS A 'BASIN'

Since all criteria the diagnosis major depression is based on may vary, it covers a great many, if not most, depressive syndromes. No surprise, then, that the majority of hospitalised depressed patients are discharged with that diagnosis. Major depression is, what we have emphasised repeatedly, a 'basin' and what Parker calls a 'clinical domain'. Phrased differently, the validity of that diagnosis is low indeed. This has and has had major negative consequences for biological psychiatry. One of these is that the chance of ever finding the biological determinants of a diagnostic basin-like major depression is as great as clarifying the pathophysiology of the 'diagnosis' cardiac disorders.

The consequences for psychopharmacology are equally serious. In all likelihood, the near future will bring antidepressants with greater biological specificity or that act on neuronal

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circuits other than those currently affected. It is to be expected that those compounds will differ clinically as well or show greater clinical specificity. Those differences will remain hidden as long as the present diagnostic system is in use.

A categorical system should provide categorical answers to the question, 'who is ill (in this case depressed) and who is not?' The DSM system fails to provide those answers. No wonder that in psychiatry such answers are illusory – sharp borders do not exist; diagnostic entities shade off into one another. Many symptoms we observe in psychiatric patients, moreover, also occur in the normal population. As a consequence, test groups in depression research will oftentimes comprise individuals that would be considered to be depressed (at least by some experts), as well as individuals that are just sad (at least according to some experts). In view of this state of affairs one has to be an incorrigible optimist to hope for substantial progress in the search for the biological determinants of psychiatric (in this case depressive) disorders.

THERE SHOULD BE FUNCTIONALISATION OF DIAGNOSIS

For the time being, however, the DSM system should not be abandoned. It would revive the confusion that existed prior to DSM-III. However, the system should be fundamentally extended and refined. The way to that end I have called *functionalisation of diagnosis* (van Praag, 1997; van Praag, de Kloet and van Os, 2004). I propose a step-wise process. The first step is the DSM diagnosis. This provides no more than a global diagnostic indication. Next, the syndrome is defined. This diagnostic information is also far from precise. Syndromes often appear in incomplete form and many patients suffer simultaneously from more than one complete or incomplete syndrome. Hence, a third diagnostic step – functionalisation of diagnosis – seems to me crucial. Functionalisation means defining first of all the psychopathological symptoms constituting the syndrome and next – most importantly – examining and if possible measuring the psychological dysfunctions underlying the psychopathological symptoms. Psychopathological symptoms and psychic dysfunctions are not synonymous. The psychopathological symptom is the way the psychic dysfunction is experienced by the patient and observed by the investigator. The last step I consider to be quintessential. If no methods are available to measure the assumed dysfunctions, they should be developed.

The advantages of functionalisation are many: it will make psychiatric diagnosing more precise, more scientific and more attuned to goal-directed biological studies and focused therapeutic interventions. It will be more precise and scientific because psychic dysfunctions are much more measurable than disease categories and syndromes, often even quantitatively. This approach will also provide the diagnostician with a detailed chart of those psychic domains that function abnormally and those functioning within normal limits. Ultimately, this approach will lead to what I have called a psychiatric physiology, a detailed chart of brain dysfunctions underlying abnormally functioning psychological regulatory systems. Biological studies as well as treatment procedures can be focused on those components of the psychic apparatus that are dysfunctioning. Furthermore, determining the cut-off points between health and disease will become feasible, based on functional criteria (e.g. is the complaining individual patient capable or not to continue his or her professional, familial or social activities as before).

Appropriate measuring instruments have to be developed. Pragmatically defined health/disease borders are by no means uncommon in medicine. The fact that a blood pressure higher than 120/80 is considered to be abnormal is not written in stone but based on data indicating that higher values increase the risk of heart and brain calamities.

Finally, the functional approach would resolve the so far unsolvable problem of distinguishing mood from anxiety disorders. In each and every patient it would become clear to what extent mood lowering and anxiety contribute to the clinical picture.

DATA ON PERSONALITY STRUCTURE AND FUNCTIONING SHOULD BE INCLUDED

I fully agree with Parker that data on personality structure and personality (dys)functioning as well as a measure of stress burden should be included in (depression) diagnosis. This information, however, will be neither relevant in determining 'caseness' nor in distinguishing (depressive) subtypes. It is relevant in determining whether or not structured forms of psychotherapy or social intervention should be included in the therapeutic programme.

DIAGNOSTIC METHODOLOGIES SHOULD BE USEFUL

A final comment: research methodology is routinely scrutinised as to its usefulness. The same should be the case with diagnostic methodology – particularly so, in a branch of medicine with so few objective, measurable diagnostic criteria. If this does not happen scientific progress will be seriously compromised.

REFERENCES

van Praag, H. M. (1997) Over the mainstream: diagnostic requirements for biological psychiatric research. *Psychiatry Research*, **72**, 201–212.

van Praag, H. M., de Kloet, R., and van Os, J. (2004) *Stress, the Brain and Depression*, Cambridge: Cambridge University Press.