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Subtyping depression by clinical features: the Australasian database

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Objective: To distinguish psychotic, melancholic and a residual non-melancholic class on the basis of clinical features alone. Previous studies at our Mood Disorders Unit (MDU) favour a hierarchical model, with the classes able to be distinguished by two specific clinical features, but any such intramural study risks rater bias and requires external replication.
Method: This replication study involved 27 Australasian psychiatrist raters, thus extending the sample and raters beyond the MDU facility. They collected clinical feature data using a standardized assessment with precoded rating options. A psychotic depression (PD) class was derived by respecting DSM-IV decision rules while a cluster analysis distinguished melancholic (MEL) and non-melancholic classes.
Results: The MELs were distinguished virtually entirely by the presence of significant psychomotor disturbance (PMD), as rated by the observationally based CORE measure, with over-representation on only three of an extensive set of 'endogeneity symptoms'.
Conclusion: In comparison to PMD, endogeneity symptoms appear to be poor indicators of 'melancholic' type, confounding typology with severity. Results again support the hierarchical model.

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Introduction

Over the last decade, research at the Mood Disorders Unit (MDU) in Sydney has focused on distinguishing psychotic depression and melancholic depression from a more heterogeneous residue of non-melancholic depressive disorders on the basis of clinical features. Early studies identified the importance of behaviourally rated psychomotor disturbance (PMD) as a 'core' feature distinguishing psychotic and melancholic depression from non-melancholic depression, with the final development of the then-labelled 'CORE' measure of PMD occurring in the CORE-II study of 413 patients (1, 2). The measure has three scales, assessing a central 'non-interactiveness' (or cognitive processing) dimension, as well as motoric 'retardation' and 'agitation', with the final CORE score being the summed scale scores.

In the development study (2), a total CORE score of 8 or more was found to be an efficient cut-off score for distinguishing melancholic from non-melancholic depression. We examined whether PMD (as so defined) was both 'necessary and sufficient' for the definition of melancholia (3). 'Necessary' meant that all those with 'true' melancholia would score above the cut-off score and, examined against three measures of melancholia: (respectively, in relation to DSM-III-R, Newcastle and MDU 'clinical' criteria) 51%, 73% and 85% of the sample met that criterion — a reasonable but not perfect result. 'Sufficient' meant that the CORE score alone would predict diagnostic allocation without any additional benefit from the addition of a set of endogeneity symptoms. Analyses revealed that, once the CORE score was entered as a predictor, diagnostic class allocation was not improved by

adding the endogeneity symptom predictor set in a logistic regression analysis. It was slightly improved, however, in relation to DSM-III-R allocations when analysed using a neural network (4).

Subsequently, the MDU recruited another sample of 269 depressed in-patients and out-patients (the PAL study). As in the CORE-II study, each of the so-called endogeneity symptoms failed to show distinct specificity to the psychotic, melancholic or non-melancholic depressive classes (5). For example, anhedonia was reported by 97%, 100% and 88% of those class members, respectively, suggesting that it was an ubiquitous feature. Several other endogeneity symptoms showed a gradient (e.g. terminal insomnia being reported by 67%, 53% and 43%, respectively) in being more common in psychotic and melancholic depression, but still common in non-melancholic depression. If any such endogeneity symptom has true specificity to melancholia, it should not have been reported by any non-melancholic subject. We therefore argued (as in the previous study) that the endogeneity symptoms more reflect variation in the severity or expression of the underlying mood state component shared across all depressive disorders rather than having any distinct subtyping capacity.

The distinction between melancholic and non-melancholic depression in this PAL sample was again driven principally by observationally rated psychomotor disturbance (PMD) — as quantified by the CORE measure. PMD strongly met both 'necessary and sufficient' criteria here, suggesting its impressive efficiency as a discriminator as well as indicating that endogeneity symptoms were redundant in distinguishing melancholic and non-melancholic depression once CORE scores were considered. Distinction of psychotic from melancholic depression in the CORE-II study was driven by the specific presence of psychotic features, but assisted by significantly greater PMD, and a significantly greater chance of the subjects reporting appetite/weight loss, terminal insomnia and constipation. In the PAL study, however, only the presence of psychotic features and the greater severity of PMD distinguished psychotic from melancholic depression.

If confirmed, the identification of features having class specificity, as against merely being over-represented in psychotic and melancholic depression, allows a hierarchical model (detailed later) for distinguishing the three classes more incisively, while also assisting the development of efficient subtyping algorithms.

As both studies have involved ratings by MDU research psychiatrists only, it is possible that results may have been driven by a response bias. Thus, if the MDU psychiatrists were sufficiently sophisticated as clinicians to validly distinguish melancholic and non-melancholic depression, they might 'rate up' the presence of PMD in the former group and 'rate down' in the second group, so contriving the suggested efficiency of CORE-rated PMD. As a consequence, we re-examine the postulates using a wider sample of Australasian psychiatrist raters, and examine whether earlier results are replicated. Here (in our Australasian Data Base, or ADB, study), regional psychiatric clinicians and researchers were requested to collect clinical data on patients with a clinical depressive episode and according to a structured format. The dataset required CORE measure ratings, but the non-MDU psychiatrists did not receive any direct training in the CORE system. The derived database thus provides a third (and presumably more heterogeneous) sample for identifying those clinical features that might best distinguish psychotic, melancholic and non-melancholic depression.

Material and methods

Procedure and sample

Interest in participating in the ADB was canvassed via direct mailout and given publicity in a variety of professional meetings. Those psychiatrists expressing interest received written details about the study design, protocols, potential uses of the database and a complete interview kit. The psychiatrists were requested to enrol (consecutively, randomly or on some regular basis such as day/week) patients presenting with a significant depressive disorder (either first episode or a first presentation of a new episode). Contributing patients and psychiatrists were given ID numbers, and no identifying details were collected on any patient, while Ethics Committee clearances were obtained from relevant institutions. Recruitment occurred over a 2-year period, with a total of 385 forms returned. Substantively incomplete data resulted in 16 forms being excluded, with current analyses undertaken on the remaining 369 subjects contributed by 27 psychiatrists (with five fully trained in the use of the CORE measure).

The dataset

'Form A' was completed by the patient and sought data addressing sociodemographic variables together with information on medical problems, lifetime depression, mood state items for the current depressive episode and details on depressive symptoms judged as able to be assessed by self-report.

Some of these data allowed binary ratings (e.g. yes vs. no) and some used dimensional ratings (e.g. assessing the persistence of any feature across the day, or its severity, with the latter generally using four-point rating options).

'Form B' was completed by the psychiatrist. In addition to obtaining further details on lifetime depressive and (any) manic episodes, items requiring sophisticated clinical assessment were included (e.g. family history of depression, symptoms such as 'distinct quality', psychotic features, whether the depression was primary or secondary). For a number of items (e.g. loss of interest, anhedonia, guilt, shame), precise definitions were given, although four-point rating options of severity or persistence were preserved. In addition, categorical rating options were provided for some items. For example 'over-valued ideas' were distinguished from 'possible delusions'. Identification of any delusion then required choosing between mood congruent and mood incongruent options, while a category allowed for delusions that occurred 'in the context of a distinct borderline personality'. A similar subdivision occurred for hallucinations. Guilt was first rated as being present or not. If present, assessment required judging whether it was explainable in terms of the patient's personality and/or current circumstances. If more severe than warranted by those factors, it could then be rated as 'severe' (but not marked by morbid remorse), at the level of an 'over-valued idea', or at a 'delusional' level.

The interviewing psychiatrist was required to complete the CORE measure of PMD according to the standardized printed instructions (2) and complete a 17-item Hamilton form (6), while the patient was requested to complete the AUSSI (Affect Underpinned by Severity and Social Impairment) State Depression Measure (7), a measure of both mood severity and disability with a combined total score. Psychiatrists were not required to make a clinical or formal diagnosis. Subsequently, an algorithm allowed DSM-IV diagnoses to be generated on returned datasets.

Statistical analyses

In contrast to our two previous studies — where we have used latent class analysis — here (after deleting the 28 PDs) we used a K-means cluster analysis (with a two-cluster solution imposed) as our principal strategy to distinguish melancholic and non-melancholic depressed subjects. Comparison of clinical features was made by *t*-tests and chi-square analyses.

Results

Characteristics of the sample

The 369 subjects comprised 235 (64%) females, with a mean age of 45.7 (SD 16.3) years; with 95 (26%) being single, 175 (47%) being married or in a *de facto* relationship and 99 (27%) being separated, divorced or widowed. Seventy-seven (21%) were in full-time employment, 90 (24%) were involved in home duties or had part-time employment, 14 (4%) were students, 110 (30%) were receiving a pension or sickness benefits, 31 (8%) were retired and 47 (13%) were unemployed. The average duration of the current depressive episode was 75 (SD 150) weeks, 365 (99%) judged that their mood state was associated with significant functional impairment and 280 (76%) judged that they were at or near the episode nadir in terms of severity. Forty-three (12%) were judged as having had a previous manic, hypomanic or mixed episode 'definitely' or as 'highly probable', and a further 46 (13%) as 'possibly' having such a bipolar history. A family history of likely psychotic or melancholic depression was recorded for 161 (44%) of the subjects.

DSM-IV diagnoses

All 369 patients met the symptom required by DSM-IV for major depression; 386 (98.6%) had been depressed for a minimum of 2 weeks, one for only 1 week, while duration data were missing for another four patients. Of those with major depression, 28 (7.6%) had the specifier of 'psychotic features', 119 (32.2%) the specifier of 'melancholic features' and 269 (72.9%) had a 'recurrent' major depression.

Distinguishing those with psychotic depression

As the DSM-IV criteria for major depression with psychotic features include delusions and/or hallucinations, and as these features were the only ones to show specificity in the PAL study, we assigned 28 subjects to such a 'psychotic depression' (PD) class by the presence of one or both features.

Distinguishing melancholic from non-melancholic depression

For the cluster analysis, six 'endogeneity symptoms' (i.e. non-reactive mood, loss of interest or anticipatory anhedonia, consummatory anhedonia, appetite and/or weight loss, diurnal mood variation, terminal insomnia) examined in our previous studies were included in the endogeneity item set, in addition to the total CORE score quantifying PMD. That analysis assigned 98 (26.6%) to a putative melancholic ('MEL') cluster and 243 (65.8%) to the residual non-melancholic

('non-MEL') cluster. Assignment was predictably in agreement with DSM-IV assignment for the PDs. DSM-IV and cluster solution-assignment to melancholic and non-melancholic classes were in moderate agreement only (i.e. of the non-MELs, 75% were so assigned by DSM-IV rules, and of the MELs, 66% were so assigned by DSM-IV), giving an overall classification agreement of 72.4%. In Table 1 and subsequent tables, we examine for (i) overall group differences, (ii) differences between PD and MEL subjects and (iii) differences between MEL and non-MEL subjects. Such analyses provide an opportunity to determine whether our class 'cleavage' rules generate clinical pictures compatible with the 'givens' for psychotic and melancholic depression.

Because of the large number of analyses, we applied a Bonferroni correction to determine whether or not differences were significant. No differences were established between PDs and MELs for Table 1 variables. Comparison of MELs and non-MELs established that the non-MELs were younger (and presumably with that age difference driving differences evident on marital status and employment variables), developed their first depressive episode (and received initial treatment) at a younger age and had had more depressive episodes. Group differences were not identified on the family history of depression or life event variables, or in reporting an antecedent life event stressor. The PDs scored non-significantly higher on the Hamilton than the MELs (presumably reflecting the psychotic items in the Hamilton scale) who, in turn, scored higher than the non-MELs (again presumably reflecting inclusion of the observable psychomotor items in the Hamilton scale). The non-MELs scored

Table 1. Comparisons of demographic and depression history variables across psychotic, melancholic and non-melancholic classes

	Class						Contrast	
	Psychotic ($N=28$)		Melancholic ($N=98$)		Non-melancholic ($N=243$)			
Variable	%	Mean	%	Mean	%	Mean	Psych vs. MEL	MEL vs. non-MEL
Socio-demographic								
Age		55.9		53.0		41.6		$t=6.2$**
Gender: female	67.9		60.2		64.6			
Marital status								
Married/*de facto*	42.9		50.0		46.9			
Separated/divorced	14.3		21.5		18.9			
Widowed	25.0		12.2		3.7			
Never married	17.9		16.3		30.5			$\chi^2=14.6$*
Employment								
Full time	10.7		17.3		23.5			
Part time	0.0		6.1		11.1			
Home duties	14.3		16.3		9.1			
P/t work + home duties	0.0		0.0		6.2			
Student	7.1		1.0		4.5			
Pensioner/sickness benefits	46.4		31.6		27.2			
Retired	14.3		16.3		4.5			
Unemployed	7.1		11.2		14.0			$\chi^2=28.0$**
Years education completed		10.7		11.6		13.4		$t=-3.8$**
Depression history								
Family history (dep/bipolar/psych)	37.0		52.1		42.1			
Age at first depression episode		39.1		34.0		25.6		$t=4.3$**
Age first treated for depression		36.7		39.0		29.8		$t=4.4$**
Age first clinically significant dep		41.1		38.0		28.6		$t=5.1$**
Number of lifetime episodes		7.5		7.7		18.0		$t=-3.6$**
Hospitalized for previous episode	63.0		54.1		44.0			
Suicide attempt — past episode	21.4		20.4		25.1			
Life events								
Stressful events in 12 months prior dep	64.3		77.6		78.6			
Severity of stressful life events		3.3		3.4		3.4		
Severity of acute stressors		2.3		2.5		2.5		
Severity of enduring circumstances		2.1		2.3		2.4		
Depression severity								
AUSSI mood		12.3		12.6		11.5		
AUSSI disability		9.9		9.9		7.8		$t=4.4$**
AUSSI total		22.2		22.4		19.4		$t=3.1$**
Hamilton		27.7		24.9		18.7		$t=9.2$***

Under Bonferroni correction, * $\leqslant 0.025$; ** $\leqslant 0.005$; *** $\leqslant 0.0005$.

as less depressed on the AUSSI Disability Scale and total score.

In Table 2 we tabulate clinical feature data to determine those features distinguishing the derived classes. Most prevalence data for dimensional items contrast those who scored '3' or '2' (i.e. severe or moderate), against those who returned or received a '1' (mild) or '0' (absent) rating — as inclusion of a '1' rating made some endogeneity symptoms virtually ubiquitous across the sample.

Comparison of the PDs and MELs indicates that delusions (whether examined as an overall category, or within subcategories of guilt, shame or the sense of feeling 'deserving of punishment') were essentially ubiquitous to the PD class (i.e. delusions being elicited in 86% and hallucinations evident in 32% of the PDs). In addition, the PDs returned higher CORE scores than the MELs (total scores = 19.9 vs. 16.4), contributed principally by higher agitation and non-interactiveness CORE scale scores. For the remaining features, the prevalence data for the PDs and MELs were very similar — both for commonly regarded endogeneity symptoms as well as for psychomotor disturbance when assessed as a symptom.

We then examined the extent to which PMD was specific to melancholia. A latent class analysis of the CORE signs revealed a similar pattern of probability loadings as revealed in the CORE-II and PAL studies. This is an important finding in indicating a similar structure to the CORE signs across independent samples. A logistic regression suggested that a CORE cut-off of 9 was optimal in distinguishing two subgroups on the basis of CORE scores, thus almost identical to the 8 or more cut-off derived in the CORE-II study. In this ADB sample, comparison of the MELs and non-MELs demonstrates distinctly higher CORE scores in the MELs (i.e. 16.4 vs. 4.1). As our optimal cut-off in this study (of 9 or more) was close to that derived in the CORE-II development study, we preserved the latter (i.e. 8 or more) here

Table 2. Comparisons of symptoms and signs for current depression episode across groups where 'Psychotic' group based on delusions/hallucinations, then 'Melancholic' and 'Non-melancholic' depression derived from cluster analysis

		Classes						Contrast	
		Psychotic		Melancholic		Non-melancholic			
		($N=28$)		($N=98$)		($N=243$)			
Variable	Total sample prevalence (%) or mean	%	Mean	%	Mean	%	Mean	Psych vs. MEL	MEL vs. non-MEL
Symptoms									
Appetite/weight loss	68.4%	81.5		72.4		65.3			
Mood worse a.m.	32.0%	30.8		32.0		32.1			
Anhedonia	55.9%	60.7		57.1		54.8			
Terminal insomnia	58.8%	66.7		61.5		56.8			
Loss of interest	83.4%	82.1		93.9		79.3			$\chi^2=10.7^{**}$
Non-reactive mood	67.4%	82.1		77.6		61.5			$\chi^2=8.0^{*}$
Non-varying mood	18.0%	42.3		24.7		12.8			$\chi^2=7.3^{*}$
Feels physically slowed	78.5%	71.4		86.7		76.0			
Feels restless	23.6%	25.0		25.5		22.7			
Mood not like bereavement	66.6%	64.3		73.5		64.0			
Loss interest in sex	65.1%	40.7		71.1		65.4			
Unpleasant thoughts	70.1%	57.1		75.5		69.4			
Concentration difficult	78.3%	71.4		80.6		78.1			
Difficult to make decisions	73.4%	64.3		78.6		72.3			
Delusions	6.5%	85.7		0.0		0.0		$>\chi^2=103.8^{***}$	
Hallucinations	2.4%	32.1		0.0		0.0		$\chi^2=33.9^{***}$	
Guilt, severe	20.3%	7.1		26.5		19.3			
Guilt, over-valued idea	8.4%	14.3		19.4		3.3			$\chi^2=24.8^{***}$
Guilt, delusional	2.7%	35.7		0.0		0.0		$\chi^2=38.0^{***}$	
Shame, delusional	2.2%	28.6		0.0		0.0		$\chi^2=29.9^{***}$	
Deserving of punishment, over-valued idea	6.0%	17.9		13.3		1.6			$\chi^2=19.9^{***}$
Deserving of punishment, delusional	1.6%	21.4		0.0		0.0		$\chi^2=22.0^{***}$	
Constipated before medication taken	14.2%	21.4		17.3		12.0			
Signs									
CORE: scale scores									
Non-interactiveness	3.15		7.8		6.2		1.4	$t=3.7^{***}$	$t=20.9^{***}$
Retardation	3.60		7.9		7.3		1.6		$t=20.6^{***}$
Agitation	1.85		4.2		2.9		1.2	$t=3.5^{***}$	$t=7.9^{***}$
Total CORE mean score	8.60		19.9		16.4		4.1	$t=3.8^{***}$	$t=24.2^{***}$
CORE $\geqslant 8$	45.8%	100		100		17.7			$\chi^2=195.1^{***}$

Under Bonferroni correction, $^{*}\leqslant 0.025$; $^{**}\leqslant 0.005$; $^{***}\leqslant 0.0005$.

— with all PDs and all MELs in this ADB study scoring above that cut-off, against 18% of the assigned non-MELs, suggesting quite impressive specificity of PMD to melancholic and psychotic depression. By contrast, when psychomotor disturbance was assessed as a symptom, no differences were evident across the MELs and non-MELs — with 87% and 76% respectively reporting that they felt slowed down, and 25% and 23% respectively reporting feeling restless.

Most of the endogeneity symptoms showed distinct prevalences in both the MEL and non-MEL clusters, indicating lack of specificity to melancholia. While several were significantly more likely in the MELs (i.e. loss of interest, non-reactive mood, non-varying mood, over-valued ideas of guilt and being deserving of punishment), others (i.e. loss of appetite and weight, diurnal mood variation, anhedonia, terminal insomnia) were non-differentiating.

As in our two previous studies (CORE-II and PAL), we sought to examine the comparative utility of CORE-rated PMD and endogeneity symptoms to the definition of melancholia. In the CORE-II study, we first examined for associations between a refined set of endogeneity symptoms (i.e. appetite and/or weight loss; mood and/or energy worse in the morning; anhedonia; terminal insomnia; loss of interest; and non-reactive mood) and total CORE scores, with individual correlation coefficients ranging from 0.25 to 0.50 (and thus suggesting some overlap or shared variance). In this study, all such associations were trivial or non-existent for those features. The lack of any association between CORE scores and the endogeneity symptom set indicated that there was no shared variance, and that there was little likelihood of the symptom set predicting melancholic status. In further analyses, we regarded the six endogeneity symptoms as forming a polythetic set (i.e. each symptom essentially being regarded as of equivalent weight to the other). We thus sought, as in recent DSM manuals, to determine the optimal cut-off in symptom numbers for differentiation. All possible cut-off scores (ranging from 1 or more to all six symptoms) suggested poor differentiation (quantified by low kappa coefficients, ranging from 0.00 to 0.09). That is, no cut-off could be derived in symptom numbers that differentiated MEL or non-MEL status to any degree. By comparison, using the criterion of a CORE score of 8 or more (derived in the CORE-II study as a cut-off score for MEL and non-MEL defined by latent class analysis) produced a kappa coefficient of 0.73. Thus, PMD demonstrated strong specificity, while all endogeneity symptom sets lacked specificity.

Discussion

As noted in the introduction, we have previously reported two studies similarly seeking distinction between psychotic, melancholic and a residual non-melancholic class on the basis of clinical features. In both, distinction between the two latter classes has appeared largely determined by the presence of observer-rated psychomotor disturbance (PMD) as assessed by the CORE measure. The concern about such studies is one of observer bias — that the MDU research psychiatrists might rate the CORE measure so as to derive such a result, whether conscious or not of any such rating bias. The identified specificity of CORE-rated PMD to the melancholic class established in this study argues against any MDU bias determining idiosyncratic results in the earlier study. A second concern about the two previous samples is that they have been derived from patients attending our tertiary referral MDU, obviously weighting samples to patients with severe and treatment-resistant conditions, and presumably increasing the representation of those with true psychotic and melancholic depression.

By establishing the ADB or clinical panel, we sought to widen clinical assessment outside MDU clinicians and obtain a more heterogeneous sample. A limitation was that most of the non-MDU psychiatrists were not trained in the CORE system. The CORE rating sheet, however, had precise descriptors of each item together with clearly identified anchor points. While 22 non-MDU psychiatrists did contribute patients to our current sample, there was the informal impression of disproportionately higher returns from academic psychiatrists working in services assessing patients not necessarily that different from the MDU service. Nevertheless, if we compare the identified prevalence of the three classes across the two MDU samples (CORE-II and PAL) with the current ADB sample, we find respective prevalences of 10%, 11% and 8% for the PDs, and 45%, 34% and 27% for the MELs. Thus, the current sample strategy did result in a lower representation of putative PDs and MELs. Other variables constant across the studies (e.g. mean Hamilton scores, lifetime number of episodes, etc.) also suggested that the current sample was (overall) slightly less severely ill and disabled over time by their depressive disorders.

The current study differed methodologically in three principal ways. For many clinical features assessed by the rating psychiatrist, we provided extremely precise definitions of terms such as ‘anticipatory anhedonia’ and went to some trouble to distinguish between qualitative and quantitative nuances of features such as guilt, which can range from normal guilt to over-valued ideas to delusional

intensity. Secondly, as our previous studies have suggested that most depressed subjects (and not merely 'melancholic' ones) will affirm nearly all of the 'endogeneity symptoms', we imposed a minimum severity rating of 'moderate' before most dimensionally assessed symptoms could be rated positively. Thirdly, we used a cluster analysis to distinguish melancholic and non-melancholic classes, whereas we have principally used a latent class analytic strategy in the two previous samples.

We respected the DSM-IV definition of psychotic depression to determine PD status, as this had been supported in our previous PAL study. While DSM-IV views psychotic depression as a subtype of major depression, we view it a subtype of melancholia (2), although we have not resolved whether it is a more severe or differing expression of melancholia. Current results also favour viewing it as having a melancholic base. Thus, our PDs resembled the MELs on a wide range of variables (including age, age of onset, number of lifetime episodes and on the prevalence of most of the endogeneity symptoms).

The PD class differed from MEL by only one dimensional variable (i.e. higher mean CORE scores) and by several unique — albeit definitional — categorical variables (i.e. delusions and hallucinations), with delusions about guilt and shame showing impressive specificity. Differentiation in CORE scores was not as distinctive as in the earlier CORE-II and PAL studies, suggesting that some true PDs may have been assigned to the MEL class, an issue considered shortly. The PDs did not differ from the MELs in the prevalence of over-valued ideas. This could reflect reality or, more likely, the difficulty in operationalizing over-valued ideas on either a categorical or dimensional basis — and we clearly favour the latter explanation. Such a pattern (i.e. PD defined by psychotic features, having more severe PMD than rated in MEL subjects, and not differing by severity of endogeneity symptoms) is completely compatible with our PAL data results.

This pattern is, however, not compatible with our earlier CORE-II study, where our analyses identified some PD subjects who denied any psychotic features but had severe or profound PMD. There we hypothesized that their PMD was so severe (i.e. making them mute or otherwise uncommunicative) that they could not admit to psychotic features (which were later established after improvement had occurred), and suggested that very severe PMD should encourage the clinician to be suspicious of PD status, with severe PMD thus acting as a possible diagnostic proxy. While we pursued such a possibility in this study (by undertaking a number of cluster analyses seeking to distinguish the PDs and MELs), lack of support suggested that we should alternately respect the DSM-IV decision rules. However, previous formal classificatory systems (see 2) have allowed such a diagnosis to be made on the basis of depressive stupor alone. It is possible that there were no such patients in the ADB sample, or that our clinician raters may have pursued psychotic features assiduously in those with severe PMD.

Our cluster-derived MELs differed from the residual non-MELs on a number of the givens for that disorder (see 2). They were older (currently and at first episode), had a more severe depression, tended to have been more likely to have been hospitalized, and were more likely to have received ECT (this and other treatment nuances will be considered in another publication), although there was no suggestion that antecedent life-event stressors were less common (as would be expected if melancholia is viewed as an endogenous depression). Such differentiation on those illness course variables offers some support (in the absence of any definitive gold standard) for the view that the cluster analytic strategy did separate out melancholic and non-melancholic depressive classes. In terms of differential clinical features, the groups were then most clearly distinguished by the presence and severity of PMD, and somewhat by the over-representation of three endogeneity symptoms (i.e. loss of interest, non-reactive mood and non-varying mood). Nevertheless, the presence of the first two symptoms was also quite substantive in the non-MELs (i.e. 79% and 61%). This finding, together with the lack of differentiation effected by the other endogeneity symptoms examined, again challenges the long assumed capacity of such symptoms to define endogeneous/melancholic depression. As in our previous studies we suggest that most symptoms reflect depression severity *per se*, or if they do possess *any* greater likelihood of occurrence in melancholia, then it is either slight or confounded by difficulties in measurement.

The data from this and our two preceding studies again support a hierarchical or tiered model for distinguishing three substantive depressive classes on the basis of clinical features alone, as detailed recently (5). The model is based on cleavage between those classes (i.e. psychotic, melancholic and non-melancholic) being driven entirely by the presence of class-specific features. Thus the residual non-melancholic class has no class-specific features, with any intraclass variation being driven only by mood state severity and by varying contributions of personality or temperament style (i.e. a spectrum model). Proceeding to the next class (melancholia) the mood disorder is more severe, but the class is defined by a specific feature (i.e. observable PMD). Proceeding to the next class (i.e. psychotic depression) both the mood disorder and PMD are more

severe, but the class is defined by the specific presence of psychotic features. Thus, the system concedes long-standing recognition of varying mood severity but — as the mood state is non-specific and common to all the depressive classes — does not seek to differentiate on such a variable. We would argue that failure to recognize that latter point has confounded and limited previous attempts to define melancholia and certainly confounds the current DSM-IV definition of melancholia, with the endogeneity symptoms more measuring depression severity rather than depressive type. We supported this argument in our PAL study (5) by comparing the capacity of our CORE-based with DSM-IV decision rules for melancholia, and demonstrated clear superiority to the former approach against a range of clinical validators. Such an argument would nevertheless be advanced by further studies testing the comparative capacities of the contrasting models to demonstrate differences across a range of neurobiological measures and response to various antidepressant treatments.

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