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Defining Melancholia: A Core Mood Disorder.

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Footnote: *The Mood Assessment and Classification Committee (MAC Committee) comprised academic psychiatrists with clinical expertise in the management of mood disorders and researchers with an interest in depression and bipolar disorders. The independently convened committee specifically targeted contentious aspects of mood disorders diagnosis and assessment with the express aim of informing clinical practice and future research. Members of the committee held one face to face meeting in Sydney (Australia) to discuss the issues in depth and agree upon outcomes. These were then developed further via email correspondence.*

Keywords

Melancholia, melancholic depression, endogenous depression, psychomotor disturbance

Melancholia (qua endogenous, endogenomorphic, vital, type A depression) has long been positioned as the quintessential clinical depressive disorder, largely as a reflection of its severity, lack of obvious explanatory causes, stereotypic clinical features (that occur seemingly independent of culture), and its preferential response to physical therapies. To characterise melancholia, most

studies have focussed on unipolar (major) depression, although the depressed phases of bipolar disorder tend to be more consistently melancholic in type, albeit commonly with two atypical symptoms (i.e. hyperphagia and hypersomnia), especially in younger sufferers. Psychotic depression, defined typically by mood congruent delusions and/or auditory hallucinations, manifests characteristically with melancholic features, although diurnal variation in mood and energy may be less evident.

In practice melancholia is commonly viewed simply as a 'more severe' form of clinical depression. But, if this is the case, then its response to treatments should be akin to that of non-melancholic depressive states. However, numerous meta-analyses[1] of those with major depression (principally comprising non-melancholic states) indicate a non-specific treatment response, with all antidepressant drug classes and evidence-based psychotherapies (as well as counselling, St John's Wort and even bibliotherapy) having comparable efficacy. Thus we argue for distinguishing melancholia as a separate 'type,' because of its distinct biological underpinnings and, in comparison to non-melancholic (or major depression) sufferers, demonstrating a gradient of differential responses to differing treatment modalities that allow treatment prioritisation.

Melancholia's ascriptions include higher heritability and the greater relevance of biological factors. While there is no sufficiently accurate laboratory test for melancholia, the dexamethasone suppression test (DST) demonstrated discernible separation from non-melancholic depression – arguing persuasively for neuroendocrine perturbation – while shortened REM latency is another possible marker. Recent functional MRI research[2] implicates diminished executive network and cortical engagement - functional brain changes that relate to the anhedonia and constriction in the reactivity of mood and affect long observed in those with melancholia.

From a therapeutic perspective, melancholia shows a low placebo response rate (10%) that contrasts markedly with that quantified in trials of major depression (typically 40% - 60%). An early meta-analysis indicated that tricyclic antidepressants (TCAs) were three times more likely to be effective than selective serotonin reuptake inhibitors (SSRIs). This corroborates clinical experience, which alludes to a monotherapy[1] antidepressant gradient in which SSRIs are least likely to be efficacious, dual action medications are intermediate and TCAs and monoamine oxidase inhibitors are the most efficacious. Even more potent is electroconvulsive therapy (ECT), which is particularly beneficial for those with melancholia, but is rarely indicated first or second-line other than in cases of catatonic-like inanition. The superiority of antidepressant medication over an evidence-based psychotherapy in the treatment of melancholia has been demonstrated in several studies with

superiority of antidepressant drug therapy over cognitive behaviour therapy emerging as early as four weeks in one study[3].

A key reason as to why melancholia has not been properly characterised in recent times is that the criteria for its DSM-5 specifier are problematic. For instance, four of eight listed symptoms are required to meet the specifier threshold, but four symptoms (i.e. loss of pleasure, psychomotor agitation or retardation, weight loss and excessive guilt) are also criteria for major depression per se. Thus, the presence of a certain set of symptoms provides minimum separation of major depression with – as against without – melancholia. Logically, major depression would be defined as a depressive 'domain' in which symptoms can be weighted to all varieties of clinical depression and its melancholia specifier can have a set of differing features that are *specific to melancholia*. Not only do DSM-5 criteria for melancholia have intrinsic limitations but any study seeking to determine causes and evaluate treatments for melancholia is inherently compromised if such criteria are used, explaining in part why so many studies of contrasting treatment modalities using DSM criteria generally fail to show differential outcome data.

Failure to clearly demonstrate distinct symptom specificity clearly contributed to melancholia being marginalised in recent decades. However, many of the so-called representative 'endogeneity symptoms' that were tested in modelling studies are in reality non-specific. Thus, while those with melancholia will commonly report insomnia, appetite and weight changes, degrees of lack of pleasure and mood non-reactivity, as well as impaired concentration, such symptoms are just as likely to be reported by those with non-melancholic depressive conditions. Therefore any measure of melancholia that includes such non-specific features will effectively 'swamp' the capacity of truly differentiating features and disallow bimodality of scores (or a point of rarity) on any derived measure to be demonstrated. This is important as, if melancholia is a distinct and categorical condition, it might be expected to have specific or at least distinctly over-represented clinical symptoms and signs, and bimodality of measure scores is necessary if it is to be successfully argued that melancholia is a discrete condition.

So how best to define melancholia? For some 2000 years melancholia was viewed more as a movement disorder – as against a mood disorder, reflecting the signal presence of psychomotor disturbance (PMD), evident as a sign in all those with melancholia whose condition was of some severity. PMD is reflected in 'retardation' (so-called 'retarded depression') where the individual is physically and verbally slowed, monosyllabic in speech, shows latency in responding to questions, and is often slumped. PMD may also be expressed as agitation ('agitated depression') where the individual is usually retarded for much of the time but shows epochs of agitated behaviour (e.g.

pacing up and down, wringing their hands, showing facial apprehension,, evidencing stereotypic movements and sometimes opportuning – with repetitive distressing "What is going to become of me?" exhortations). The 'psycho' component of PMD is reflected in an inability to concentrate – and not reflecting multiple distractible worrying thoughts as experienced by many with a non-melancholic depression – but by thinking distinctly slowed and 'foggy' –and by an inability to absorb and lay down new information.

To better capture these features a sign-based CORE measure of PMD developed by Parker and colleagues[4] showed that it was superior to a representative set of endogeneity symptoms in defining melancholia and met the 'necessary and sufficient status' criterion (in that all those with 'true melancholia' had distinct PMD, while when PMD and endogeneity symptoms were used to differentiate depressive sub-type their combination was not superior to the use of CORE-generated PMD scores alone). Validity studies further supported the CORE measure (i.e. the higher the CORE score, the greater the DST non-suppression rate), while higher CORE scores predicted a superior response to ECT.

However, the study participants were generally older (and PMD increases with age in those with 'true melancholia' – being less distinctive in adolescents and young adults), while differentiating melancholic and non-melancholic depression when the individual is not at episode nadir is problematic. We therefore returned to endogeneity symptoms and refined a set across several studies. As symptoms alone only had an overall accuracy of 65%, we added illness 'correlates' for melancholic and non-melancholic depression, with examples in the box. The derived measure (the SMPI or Sydney Melancholia Prototype Index) improved overall accuracy in discriminating melancholic and non-melancholic depression to approximately 80%[5].

As clinicians it is important to weight the following symptoms and signs in allocating a diagnosis of melancholia. Firstly, PMD (with no organic basis identified) as admitted by the patient and/or as observed by a corroborative witness, with the patient stating that it is physically difficult to get out of bed, or if they do they lie on a couch and might not wash for days (i.e. anergia - a genuine lack of energy as against being amotivated). Secondly, an anhedonic and non-reactive mood, which should be absolute and/or distinctive. Third, diurnal variation, with most reporting their mood and energy as improving across the day but a minority reporting a worsening late in the afternoon and usually as the sun sets. Finally, impaired concentration, as defined earlier and often reported as 'foggy' thinking. A useful additional feature is the individual viewing their depression as imposed on them rather than as understandable in light of their personality and exposure to life event stressors, and a family history of depression and/or of suicide adds a further weighting.

Thus, we argue for a categorical model whereby melancholia is positioned as a discrete and categorical depressive sub-type (see Box 1), predisposed by genetic factors, with a set of perturbed biological functions.

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Disclosures

The authors do not have any commercial associations that may pose a conflict of interest in connection with this manuscript.

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Box 1. Proposed key symptoms and features of melancholia that differentiate melancholic from non-melancholic patients using SMPI clinician rating (Parker et al. 2013).

1. Anergia
2. Anhedonia
3. Mood and energy worse in mornings
4. Physically slowed
5. Impaired concentration
6. Weight loss
7. Disproportionate severity of depressive episodes, given circumstances
8. Absence of distinct developmental stressors
9. Depression can sometimes "come out of the blue"
10. No more likely than most people to become emotional about things
11. When not depressed, has no major difficulties in relationships
12. When not depressed no more likely than most people to worry.

Patients with Melancholia are more likely to present with:

(1) Key Symptoms (by relative loading):

I. Anhedonia and anergia, with diurnal variation
II. Psychomotor slowing
III. Impaired concentration

(2) Key Feature: Disproportionate Severity of Mood Episodes, given precipitating factors