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The doctrine of the two depressions in historical perspective

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Abstract

Objective—To determine if the concept of two separate depressions –melancholia and non-melancholia – has existed in writings of the main previous thinkers about mood disorders.

Method—Representative contributions to writing on mood disorders over the past hundred years have been systematically evaluated.

Results—The concept of two separate depressions does indeed emerge in the psychiatric literature from the very beginning of modern writing about the concept of ‘melancholia’. For the principal nosologists of psychiatry, melancholic depression has always meant something quite different from non-melancholic depression. Exceptions to this include Aubrey Lewis and Karl Leonhard. Yet the balance of opinion among the chief theorists overwhelmingly favors the existence of two quite different illnesses.

Conclusion—The concept of ‘major depression’ popularized in DSM-III in 1980 is a historical anomaly. It mixes together psychopathologic entities that previous generations of experienced clinicians and thoughtful nosologists had been at pains to keep separate. Recently, there has been a tendency to return to the concept of two depressions: melancholic and non-melancholic illness. ‘Major depression’ is coming into increasing disfavor. In the next edition of DSM (DSM-V), major depression should be abolished; melancholic mood disorder (MMD) and non-melancholic mood disorder (NMMD) should become two of the principle entities in the mood disorder section.

Keywords

affective disorders; depression; melancholia; nosology

Introduction

Clinicians have always had a gut sense that there were two depressions, melancholic depression and non-melancholic depression. These have always counted as two different diseases and not as just two forms of the same disease. An enormous mass of clinical opinion has accumulated over the years on behalf of this two-depression doctrine. Opinion is

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not the same thing as evidence, of course. Yet how to read the evidence on affective illness has proven highly contentious, while the momentum of opinion is clear for all to see.

What to call the two depressions? Melancholia constitutes a robust historical description of one of them, with well-defined boundaries and homogeneous content. ‘Non-melancholia’ as a description of the other depression is problematic because it defines a category by what it is not. In reality, non-melancholia is a mixture of dysphoria, anxiety, and depressive character. It is proposed here that it be called ‘non-melancholic mood disorder’ (NMMD). Non-melancholic mood disorder, to be sure, does not well define the contents, but the contents of everyday dysphoria and anxiety are so disparate as to be not well definable, and NMMD is a slight improvement upon non-melancholia. This analysis follows a long tradition of refusing to recognize a basic distinction between unipolar and bipolar disorders. Recently, Michael Alan Taylor and Max Fink have reported, ‘The scientific evidence fails to distinguish unipolar and bipolar depressive disorders’. ‘A revival of the concept of a single manic-depressive illness (MDI) with the depressed phase recognized as “melancholia” is… parsimonious and best fits the evidence’ (1).

This proposal for dealing with the two depressions thus abolishes entirely the diagnostic term ‘depression’, which has been bent signally out of shape by decades of abuse. It is no longer meaningful to refer to a patient simply as ‘depressed’. We should replace the label major depression and depressive episode with the term melancholia, when symptoms and signs of melancholic illness are present. The expression ‘depression’ now has the same scientific status as ‘vapors’, ‘nervousness’, and ‘madness’, having secured a post in popular medical folklore while bereft of the specificity associated with medical diagnosis.

The current proposal merely makes formal an alternative tradition in psychiatry, represented by such researchers as Ole Rafaelsen, Professor of Psychiatry in Copenhagen, of shunning the term depression and insisting on melancholia. Per Bech and Rafaelsen had a ‘melancholia’ scale and not a depression scale (2).

It was DSM-III in 1980 that committed the classic historical blunder of lumping the two depressions together in the form of ‘major depression’. This has been a nosological catastrophe from which almost 30 years later the field has not recovered. In 1983, Bernard Carroll, then at Duke University, saw the problem barreling down on the field like an express train. At a conference in Dahlem, a suburb of Berlin, he said, ‘in the clinic… some unfortunate things have happened. A conceptual drift of alarming proportions has occurred in the name of diagnostic reliability. This drift threatens to retard the field by increasing the variance present in clinical populations… As a result, new problems of epistemology and methodology have been created. How is a theory of depression to be developed, how is it to be tested, and how is an antidepressant drug effect to be recognized if the clinical entity… no longer corresponds to the original [melancholia]?’ (3) At another conference in Copenhagen, three decades later, these questions remain as pressing as ever.

The doctrine of the two depressions: origins

Thus, the issue of the two depressions is posed anew. The German psychopathologic tradition cries out for us to use the term ‘disease’, or Krankheit. Are there two different depressive diseases, as unalike as tuberculosis and mumps? The Cross-Atlantic nosological tradition has always been more cautious about ‘disease’ in psychiatry and has preferred the term ‘syndrome’. Is there a melancholic syndrome and a non-melancholic syndrome, with important biologic differences between the two? The answer of history is pretty clearly, yes.

Patients have always known, too, that there were two different forms of being out of sorts. In 1742, English poet Thomas Gray wrote to a friend, ‘Mine, you are to know, is a white melancholy… which though it seldom laughs or dances, nor ever amounts to what one calls joy or pleasure, yet is a good easy sort of a state, and ça ne laisse que de s’amuser. The only fault of it is insipidity, which is apt now and then to give a sort of ennui, which makes one form certain little wishes that signify nothing. But there is another sort, black indeed, which I have now and then felt… It believes, nay, is sure of every thing that is unlikely, so it be but frightful; and, on the other hand, excludes and shuts its eyes to the most possible hopes, and everything that is pleasurable’ (4). These were two depressions indeed, non-psychotic and psychotic, that beat within the poet’s breast as two different illnesses.

In Gray’s time, the medical classification of depression was simple. There was melancholia, then roughly a synonym for madness but harboring in its core what we would consider genuine melancholic illness; and there was ‘spleen’, a contemporary term for being downcast and out of sorts.

The medical diagnostics of the 19th century captured this dichotomy between two distinctive types of affective illnesses in the contrast between ‘neurasthenia’ and ‘melancholia’, Neurasthenia, a term popularized by the American electrotherapist George Beard in 1869 and after, became quickly expanded from the core concept of ‘tired nerves’ to mean garden-variety depression and anxiety (5) As Paris psychiatry professor Gilbert Ballet explained in 1911, there was melancholia, characterized by motor and intellectual slowing and by ‘a painful feeling of powerlessness that explains the sadness’. But then neurasthenia existed as well, a quite different phenomenon including pain, fatigue, and hypochondriac anxiety. Melancholia came on episodically; neurasthenia was more chronic (6).

Initially in medical discourse, the term ‘depression’ indicated one type of affective illness, ‘melancholia’ the second. It was Danish neurologist and pathology professor Carl Lange in Copenhagen who in 1886 was among the earliest to introduce the term ‘depression’ to psychological medicine. By depression he meant out-patients who were constantly close to tears, enervated, unable to function at work or make decisions and who manifested a ‘lack of spirits and joie de vivre as their constant complaint’. They shunned social intercourse as requiring too much effort and, often anxious, complained of an ‘indescribable feeling of apprehension’. None of his hundreds of such depressed patients had ever developed ‘melancholia’, by which he meant psychotic depression. Lange’s (1886) Danish work has been translated by Schioldann (7). Thus, Lange was clearly differentiating between psychotic and non-psychotic forms of depressive illness, but he used the term ‘depression’

as opposed to ‘melancholia’. Other authors, of course, would admit non-psychotic forms of melancholia as well. Yet with Lange, the dividing line between illnesses called ‘depression’ and ‘melancholia’ was crisply drawn.

Among the classical nosologists, the writer whose work has influenced posterity most significantly was Emil Kraepelin, Professor of Psychiatry, first in Heidelberg, then in Munich. In the sixth edition of his textbook in 1899, Kraepelin announced the existence of ‘MDI’, a massive structure that subsumed all forms of melancholia, psychotic depression, and serious depressive and manic illness of whatever stripe (8). Since then, Kraepelin’s name has been associated with the doctrine of ‘one depression’. But this is wrong.

Within Kraepelin’s magisterial structure of MDI, there was one outlier: ‘psychogenic’ depression, not a part of MDI. Psychogenic depression did not correspond to ‘simple depression’, the mild form of MDI. Rather, psychogenic depression was not autonomous; unlike MDI it did not come out of the blue; unlike MDI it was also responsive to changes in the patient’s social situation. ‘A number of patients have been referred to me’, he wrote, ‘whose deep sadness, paucity of speech and anxious tension might have suggested a circular depression; yet it came out subsequently that we were dealing with dysphorias (Verstimmungen) caused by serious mistakes (the patient had made) and by looming legal procedures. Because the milder depressions of MDI, as much as we can tell, fully resemble the motivated dysphorias of healthy psychic life – with the essential difference that they occur without motivation – in cases of this kind one will not be able to interpret the symptoms correctly without knowledge of the patient’s history (8). Kraepelin’s psychogenic depression, therefore, marks a reinforcement of the melancholic–non-melancholic distinction, one almost entirely ignored by historians of nosology.

Nosological guideposts

In our own time, the classification of depression has become vastly complicated. Many different pairings have been proposed, as though one were dealing with mere clinical variants of the same illness: mumps with swollen and non-swollen parotid glands. This great mushrooming has proven vexatious for the nosologists. There cannot be 20 different depressions; it is also unlikely, as DSM proposes, that there is just one, called ‘major depression’. Can we not do better here?

The great proliferation of depression classifications occurred because authors were looking mainly at current symptom picture and history of current illness. Many characteristics attracted the gaze of the nosologist: Did stress precipitate the illness? Had the patient previously been well? How severe was the depression? Was the patient psychotic? Did he or she have a depressive personality? Considering these features as fundamental nosological guideposts produced a riot of classifications. According to R. E. Kendell in 1976, ‘the complexity, and the absurdity, of the present situation are vividly illustrated by the fact that almost every classificatory format that is logically possible has been advocated by someone within the last twenty years’ (9).

Yet there are other nosological guideposts that physicians in the past have relied upon in sorting out illnesses. And these have played a less prominent role in the depression classifications that dot the last 40 years. These characteristics are: response to treatment, family history, and stability over time of clinical picture. Yes/no answers to these questions produce two rather clearly delineated illnesses. We will not call them depression ‘subtypes’ because they are diseases as distinct as mumps and measles. Let us call them, as suggested above, melancholic depression and NMMD. By melancholic depression we understand classical melancholia and its cousin psychotic depression (not all melancholias are psychotic). Non-melancholic mood disorders were once called ‘neurotic/reactive depression’, mixed together with a good deal of anxiety and character disorder.

Since its inception, psychological medicine has always, at some implicit and often unstated level, recognized the existence of these two depressions: melancholic and non-melancholic. The term ‘reactive’ was not introduced until Kurt Schneider suggested it in 1920 (10). ‘Neurotic’, of course, began life as a psychoanalytic category.

Endogenous depression has traditionally served as a synonym for melancholia. ‘Endogenous’ came into existence around the turn of the century as Leipzig neurologist Paul Julius Möbius proposed it for psychiatric illnesses that were inborn and untreatable (11). The argument for preferring melancholia to endogenous depression is simply that of historical steadfastness. Melancholia has borne well the vicissitudes of time and continues to delineate a homogeneous population that responds more or less uniformly to certain treatments (1).

So how about the 25 different systems for classifying affective illness that Thomas Ban identifies in an overview? (12) We can simply forget about some of them. Many classify what are essentially epiphenomena of affective illness in the most uninteresting and superficial of ways: ‘primary’ vs. ‘secondary’, or ‘major depression’ vs. ‘dysthymia’. Yet there are more solid guidelines for sorting out depression. Looking at response to treatment, biologic markers, and stability of clinical picture produces one distinct syndrome in which the affected patients do well on ECT and appropriate pharmacotherapy, tend to have the same symptoms when they relapse, and generally have positive dexamethasone suppression tests (DST). Clinically, they are very slowed and are unresponsive to good news. This is melancholic illness, and physicians have always recognized this historically.

The syndrome non-melancholic depression, or NMMD, has historically been less well demarcated and represents an admixture of unhappiness, anxiety, phobia, and character disorder (13). The patients often respond poorly to ECT and the tricyclics. If these patients relapse they may well next present with a different cluster of symptoms entirely; and little may be read from the family history. Clinically, they are all over the map, and drift as easily as not into the DSM anxiety area, or languish among the personality disorders. The syndrome, if it is one, is certainly separate from melancholia (14). [Yet the two may coexist in the same patient: patients who have endured episodes of melancholia often end up feeling demoralized. As Bernard Carroll has observed, ‘Demoralization (the giving up syndrome) resembles non-melancholic depression. So it is possible to have features of both melancholic and non-melancholic depression in one patient’; B. Carroll, personal communication].

The clinical evidence of these physicians who, over the ages, have believed in the doctrine of the two depressions is often scorned as ‘anecdotal’. Yet clinical evidence is worth something, despite a faddish contemporaneous preference for epidemiologic surveys with heterogeneous categories. The weight of the clinical experience of generations speaks strongly. If past physicians have tended, in their heart of hearts, to believe in certain clinical truths, we must at least give those beliefs, honored by the momentum of many decades of accumulated experience, a fair chance at being disproven through modern evidence-based medicine.

A critic might respond, ‘If, over the centuries, generations of physicians believed powdered cobra bladder an effective medication, does that constitute acceptable evidence of its efficacy today?’ Physicians over the years have, after all, believed many notions that the searchlight of science has shown to be demonstrably false (the phlogiston theory, bleeding, the giving of enemata, and so forth). Yet there is a crucial difference between belief in humoral doctrines laid down by Galen, and the accumulated clinical wisdom of the last hundred years or so. It is that recent generations of physicians came to believe in science as a method of finding facts rather than in inherited beliefs sanctioned by authority. Traditional medical wisdom was based on authority, on that ultimately of Galen and the doctrine of the humors. Since the mid-19th century, modern medical wisdom has been based not upon doctrines but upon hypotheses that science in its onmarch constantly sweeps away. Many of the medical beliefs of the last hundred years – not all – have survived to the present because the searchlight of evidence has not dissolved them. And in the area of mood disorders, the belief in the ‘two depressions’ is one of those recent clinical notions that seems to have stood the test of time.

The doctrine of the two depressions: recent vicissitudes

Recently, the two depressions have clashed head on. Aubrey Lewis’s 1938 critique of the division between endogenous and reactive depression was written with such brilliance that it continued to echo in the coffee rooms of psychiatry departments for decades thereafter. On the usefulness of ‘recurrence’, for example, as a differentiating factor, he wrote that it ‘may be no more indicative of an intrinsic rhythm, a biological periodicity, than is a series of colds in the head’. Lewis believed in a continuum between quite different depressions, ‘melancholia’ at one extreme, ‘neurasthenia’ at the other. Yet he despaired of further classifying gradations between them. ‘It is probably true that in some depressions the hereditary factor vastly outweighs the environmental, and that in others the reverse is the case, but to detect such cases we have only dubious means…’ (15). Lewis had the misfortune of penning his gloomy commentary on the eve of the introduction of electroconvulsive therapy. With ECT and the tricyclic antidepressants it became clear that, on the basis of response to treatment, there were indeed two different depressions and that one could make meaningful distinctions between MMD and NMMDs. Anthony Hordern, for example, distinguished between psychotic depressives, who should be treated with ECT, and ‘other depressives’, who should be given amitriptyline (16).

With the revolution in psychopharmacology in the 1950s, the school of Martin Roth at Newcastle led the reverse march away from Lewis’s single depression and back toward a two depression model. In 1959, at a conference on depression at McGill University (funded

by Geigy which had just launched imipramine in the North American market), Roth began talking of the fundamental difference between ‘endogenous depressions on the one hand and neurotic depressions and anxiety states on the other’ (17). This previewed Roth’s article in 1960 disentangling the two (18). In terms of marshalling new data in support of the two-depressions hypothesis, Roth’s student Leslie Kiloh is probably the central figure. In 1963, he and Roger Garside stated that, ‘all but one of 15 cases of endogenous depression responded well to imipramine within four weeks… whereas only 16 of 32 cases of neurotic depression were improved after four weeks’ (19) (Kiloh also re-analyzed Lewis’s depression data retrospectively and came to the conclusion that two depressions were present after all, a result he dared publish only after Lewis’s death; 20).

In the United States such investigators as Leo Hollister, the dean of American psychopharmacology in the 1960s, advocated for treatment-specific subtypes of depression. In 1965, Hollister reported that there were basically two types, endogenous and reactive (21). Endogenous responded ideally to ECT, and as a second-line treatment to TCAs or MAOIs; the reactive-neurotic-anxious group did best on phenothiazines. (This latter suggestion would later be scorned, but Hollister had seasoned clinical judgment, and the subsequent view that antipsychotics are inappropriate for NMMDs may have been premature.)

The 1960s also saw renewed efforts to distinguish endogenous from non-endogenous depression. What were the hallmarks? In 1969, Donald Klein, then research director of Hillside Hospital, and John M. Davis, chief of the unit on clinical pharmacology of the Laboratory of Clinical Science at NIMH, proposed a highly influential classification (22). On the basis of response to TCAs and ECT, they distinguished between (i) serious depressive illness, and (ii) lesser kinds of dysphoria. Serious depression, they said, was characterized by a disruption in the ability to experience pleasure. The lesser ‘depressions’ they insisted in putting in quotation marks because they did not really consider them to be depression at all (even though their patients commonly used the term).

Serious depression, they said, was manifest in a disruption of the pleasure mechanism; Klein and Davis subdivided these into retarded and agitated (Klein and Davis were, of course, not the first to distinguish between retarded and agitated depression, and Max Hamilton’s (1960) factor analysis well preceded them; 23). Then there were the lesser dysphorias, they argued. These were manifest in a variety of symptoms the authors considered mainly evidence of self-defeating and dependent neurotic behaviour. These dysphorias were subdivided into “reactive ‘depression’”, “neurotic ‘depression’”, and the ‘hysteroid-dysphoric patients’ who really became the basis of the ‘atypical’ kinds of depression that later started to emerge from the New York State Psychiatric Institute once Klein left Hillside for Columbia University. Klein and Davis did not use the term ‘melancholia’.

Outside the Cross-Atlantic community, in the years following the Second World War, the doctrine of two depressions was codified by some authorities, rejected by others. Speaking for French nosology, in 1978, Pierre Pichot of the University of Paris said that primary depression could be divided into endogenous depression and exogenous-psychogenic

depression, the former synonymous with Schneider's 'vital depression', the latter a congeries of ill-defined conditions (24).

The World Health Organization (WHO), in its ninth classification of diseases in 1975, embraced the doctrine of the two depressions by distinguishing between (i) 'affective psychoses' (by which they meant serious affective illness), a Kraepelinian construct that revolved around manic-depression, and (ii) 'reactive depressive psychosis' together with 'psychogenic depressive psychosis' (25). The WHO International Classification of Diseases (25) was based on the recommendations of the ninth revision conference, 1975 [see no. 298 ('affective psychoses') and no. 298 ('other non-organic psychoses') (25)].

The great European departure from the doctrine of the two depressions was initiated by East German psychiatrist Karl Leonhard, who in 1957 published a synthesis of his work on 'psychoses' (severe forms of illness) that had been brewing for decades. First, Leonhard announced that bipolar illness, or 'manic-depressive' psychosis, was an illness sui generis. Secondly, among serious depressions, he distinguished between 'pure melancholia' and 'pure depression'. In melancholia, the salient symptom was depressed mood (Gedrücktheit der Stimmung) plus psychomotor retardation and retardation of thought. 'Pure depression', in the Leonhard nosology, turned out to be anything but pure as there were five highly diverse subtypes, the nature of which it is unnecessary to discuss here (26).

The Leonhard system has attracted many followers. Indeed, it enjoyed in 1966 a kind of annus mirabilis, as two authorities – Jules Angst (27) and Carlo Perris (28) – endorsed the existence of MDI as separate from unipolar depression. Yet the complexity of Leonhard's thought definitely cannot be pushed onto the Procrustean bed of the two-depressions doctrine, and if Leonhard is right, then the whole subject must be rethought.

The clarity of the two depressions is muddled in DSM

It was in the United States, in events leading up to the publication of DSM-III in 1980, that the clarity of the two-depressions concept became muddled. In 1975, Eli Robins and colleagues worked out an early version of the Research Diagnostic Criteria (RDC), in which there very clearly were two depressions (in addition to bipolar disorder): major depression, with a number of subtypes including endogenous depression; and minor depression with or without anxiety (29). The RDC were formally published 3 years later, in 1978, by Spitzer, Endicott and Robins, retaining this classification and adding another depression – intermittent depressive disorder – a diagnosis made on the basis of lifetime history (30). Both versions of the RDC were sophisticated and subtle diagnostic instruments.

When DSM-III appeared in 1980 much of this subtlety, as well as the collaboration of Eli Robins, was gone (31). (Correspondence in the archives of the American Psychiatric Association (APA) shows that the input of the St Louis school into the final versions of DSM-III was minimal.) Spitzer, the architect of DSM-III, reduced the various depressions essentially to one: major depressive disorder. Another category, dysthymic disorder, would not have been inserted at all, had Spitzer not needed a diagnosis to serve as a sop to the psychoanalysts then influential in the APA. To be sure, DSM-III allowed the existence of a

'melancholic' subclass of major depression, called a 'fifth-digit code', but it was a pale shadow of full-blast melancholia. The melancholic subclass emphasized loss of pleasure and lack of mood reactivity, and buried in a long list of possible symptoms the classic melancholic feature of psychomotor change. The melancholic subclass also ignored biologic variables.

There was in fact a second depression in the pages of DSM: dysthymic disorder, a classic illness from the history of psychiatry. Yet dysthymic disorder was said in the DSM text to be coterminous with the analytic category 'neurotic depression'. As Herman van Praag has argued, major depression and dysthymic disorder were really distinctions without a difference (32), all the emphasis lay on major depression, in reality a single depression category into which almost any dysphoric patient could be squeezed. (DSM-III did acknowledge the existence of other patterns of depression, such as cyclothymic disorder and bipolar disorder. But the depression of bipolar disorder was simply major depression. It did not otherwise differ in quality.)

The two depressions re-emerge

With the appearance of DSM-III, the reaction among veteran psychiatrists was immediate against this collapsing of the two depressions into 'major depression'. In 1980, Craig Nelson and Dennis Charney at Yale commented on the 'non-specific' nature of major depression: 'The signs and symptoms of a major depressive episode appear to define a heterogeneous group that may be further divided into those patients having an autonomous depression or melancholia and those who are responsive to environmental stimuli' (33). The following year, in 1981, Max Fink found the new DSM categories 'of limited usefulness in selecting a therapy for a depressed individual' (34).

With the advent of endocrinological tests for melancholia, the existence of the two depressions was demonstrated even more emphatically. In 1981, Bernard Carroll, then at the University of Michigan, proposed the DST for the diagnosis of melancholia (35) the following year, 1982, he pointed to the high specificity of the DST in melancholia: 'Our results give unequivocal support to the view that melancholia is a categorically distinct entity from non-endogenous depression' (36). In 1990, Carroll turned the beam of the DST onto DSM-III-style melancholia. He found that the DST sensitivity to the DSM-III melancholic subclass of major depression was only 35%, the specificity was only 73%. By contrast, when the same patients were diagnosed by ICD-9 criteria, the sensitivity was 45%, specificity 96% (with the ICD-derived guidelines of the University of Michigan for melancholia, specificity was 59%, sensitivity 98%; 37).

In this manner a rift appeared in American and international psychiatry, the researchers who clung to the official DSM version of 'major depressive disorder' vs. the ever more numerous rebels who insisted on the doctrine of two depressions (at least). When in 1996, John Rush and collaborators at Texas Southwestern Medical Center at Dallas reviewed the evidence for dividing depression into biologic subtypes that could be confirmed with such biologic tests as the DST and sleep latency, they found the DST results most persuasive on behalf of the

endogenous vs. non-endogenous dichotomy that they attributed to RDC, but which in fact went back to psychiatry's beginnings (38).

In 1996, Gordon Parker and co-worker at the School of Psychiatry at the University of New South Wales in Sydney suggested a sign-based approach for the diagnosis of melancholia on the basis of phenomenology (39). In the years since, the melancholia diagnosis has gathered steam as a heritage label for an age-old concept. 'Melancholia', reported by Michael Taylor and Max Fink in their monograph on the subject, 'provides the standard on which to judge mood disorder' (40).

At the end, a question emerges that should have been asked at the beginning: What is the essence of melancholia? How do we recognize it when we see it? The question is asked at the end because it is a 'prospective' question, in that its resolution depends on future research, rather than a retrospective question we can answer with available data. In Dahlem, Carroll (1983) asked the same question: Given that many patients are recruited for depression trials through newspaper advertisements, how do we know they have 'endogenous MDD?' We don't know it, he said. 'If those patients have abnormal REM latency, REM density, or DST results to a similar extent as more typical clinical populations of endogenous depressives…' we may accept the results of trials based on these clinical groups as evidence of efficacy in endogenous depression (3). Yet those tests were largely abandoned, rather than perfected. An opportunity to sculpt out the two depressions using an endocrinological torch was lost.

This argument of the two depressions has two important practical implications. If one accepts the notion that there are two depressions, then major depression of the DSM has no longer exists. As an amalgam of the two depressions, major depression should be removed from the next edition of the Manual.

The two depressions and the pharmaceutical industry

A second application of the doctrine of two depressions concerns drug discovery. Historically, the pharmaceutical industry has been quite willing to accept the notion of various depressions. As W. Furness Thompson, research Vice-president of SmithKline & French, said in a speech in 1959, 'There seem to be several kinds of depression and they do not all respond to the same therapeutic agents' (41). Among industry insiders, it was quite common to assess agents for their impact on both melancholia and major depression. As Wyeth stated that its clinical investigators in March 1992 about venlafaxine, '…Venlafaxine is effective in treating both severely depressed in-patients with melancholia and out-patients with major depression' (42).

At one point it looked at though FDA was ready to accept the existence of two separate depressions. As FDA staffer Hillary Lee said at a meeting of the Psychopharmacologic Drug Advisory Committee in 1981, 'So one of the ways we have been going here at the FDA lately, in terms of our thinking is that these are separate… indications, and if a drug has shown effect both in in-patients and in out-patients, then we so label it, and I was thinking as a point of discussion that this drug [nomifensine] would be for out-patients' (43).

But the FDA never acted on the basis of this internal discussion. Two years later, in 1983, Paul Leber, at this point chief of the division of neuropsychopharmacology, said, 'The trouble is that no one has ever decided what the breadth of what we call depression really is… Some days we require a drug be worked up in what I will call endogenomorphic depression, to steal from Don Klein, in hospitalized patients and then we will say it is an antidepressant. On other occasions we will rely upon studies done with patients who are dysphoric, who may have a mixture of anxiety and depression…'. In general, we end up saying the drug is an antidepressant (44).

The agency's insistence on trials indicated for a single depression, major depression, has tied one hand behind the backs of medicinal chemists and clinical trialists. Because major depression is such a heterogeneous condition, whether the proposed agent beats placebo is really a matter of the luck of the draw: Agents suitable for melancholia will beat placebo only if the newspaper advertisement recruiting the patients has, somehow, managed to draw in non-suicidal melancholics. (Suicidal patients are usually excluded from trials.) Agents suitable for non-melancholic depression will fail with the melancholics, and succeed with the non-melancholics only if the newspaper advertisement has, somehow, managed to draw differentially on the reactive depressions and avoid the neurotic character disturbances.

Paul Leber is no longer with FDA, yet his remarks take in countenance the existence of melancholic depression as distinct from other varieties. Does this open the door to a pharmaceutical house interested in developing an antimelancholic medication (AMM)? (45). It would be worthwhile to find out.

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