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# Melancholia agitata and mixed depression

Koukopoulos A, Sani G, Koukopoulos AE, Manfredi G, Pacchiarotti I, Girardi P. Melancholia agitata and mixed depression.

**Objective:** The diagnostic entity of major depressive episode includes both simple and agitated or mixed depression. Mixed depression is characterized by a full depressive episode with several symptoms of excitatory nature. Mixed depressions worsen if treated with antidepressants.
**Method:** We have reviewed the clinical charts of the 2141 patients treated at the Centro Lucio Bini of Rome from January 1999 to June 2006. These patients were diagnosed according to DSM-IV criteria. Research diagnostic criteria were applied for agitated depression with motor agitation and Author's diagnostic criteria for agitated depression without motor agitation.
**Results:** One thousand and twenty-six patients had a depressive episode as index episode. Three hundred and forty six (33%) were mixed depressive states. One hundred and thirty eight (44%) of them were spontaneous; in 173 cases, the onset of the mixed depression was associated with antidepressants.
**Conclusion:** Psychic and motor agitation are considered equally important for the definition of agitated depression. Treating agitated depression with antidepressants worsens the clinical picture. The use of Electroconvulsive Therapy (ECT), neuroleptics and anticonvulsants are recommended. The term *Melancholia Agitata* is proposed for agitated (mixed) depression.

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Key words: mixed depressive states; agitated depression; melancholia agitata; antidepressants

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**Significant outcomes**

- Agitated depression should be considered as a mixed state.
- Antidepressants may worsen the agitation and the patient's suffering. ECT, antipsychotics, antiepileptics and lithium are the first-line treatment for agitated depression.
- The term Melancholia Agitata is proposed.

**Limitations**

- The study has a naturalistic, retrospective design.
- The results are preliminary.
- No statistical comparison between induced and spontaneous agitated depression has been performed.

> The inner unrest is the constant thing, the motor unrest is variable.
> Sir Aubrey Lewis, 1934

## Introduction

At present, in the globally used DSM classification, the diagnostic category of major depressive episode (MDE) includes many different depressive syndromes. All of them meet the diagnostic criteria of major depression. The most striking difference is found between depressive syndromes characterized by inhibitory symptoms and those marked by lack of inhibition and retardation and the presence of psychomotor agitation, inner agitation, racing thoughts, talkativeness, irritability, mood lability

and other symptoms of an excitatory nature. Indeed, the fifth digit of the criteria for MDE states: 'psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)'. Giving the same label to these two depressive syndromes implies that they are very similar in nature and that the difference in symptoms is not regarded as essential.

Inevitably, this has led psychiatrists to treat them in the same way. As long as ECT was the main treatment for severe depression, the difference between the two syndromes was not noted because ECT was equally effective for both. Since the introduction of antidepressant drug treatment and the decline in the use of ECT, the substantial difference in the pathophysiology of the two types of depression has become clear. Agitated or mixed depression not only manifests itself as a mixed affective state but also responds to antidepressant drug treatments with a marked deterioration in the patient's condition: increased agitation and insomnia, greater suffering and the emergence of psychotic symptoms and suicidal ideas and impulses. If antidepressants are continued, a chronic course with alternating mixed states and simple depression may develop.

There are many cases of apparently simple depression that, under the effect of antidepressants, turn into mixed depression. These cases could be recognized by the complete absence of symptoms of inhibition: we have called them cases of latent agitated depression, as it will be discussed later.

The failure to recognize mixed depression as a distinct syndrome which should be treated very differently from simple depression has dramatic consequences for many patients.

Depressive mixed states are not rare. Out of 150 manic-depressive patients, Weygandt (1) found 12 (8%) patients with agitated depression. Modern-day estimates are higher: Spitzer (2) found 29% with agitated depression; our group (3) reported a prevalence of 27% with either motor or psychic agitated depression among 361 bipolar (BP) and unipolar (UP) patients; Maj et al. (4) found 19.5% RDC agitated depressions among 313 BP I patients. Benazzi (5), defining a mixed depressive state as a major depressive episode plus three or more hypomanic symptoms, reported a prevalence of 43.9% among 144 UP and 218 BP II patients.

In the present study, 33% of 1026 MDEs were mixed depressions, distributed in all subtypes of affective disorders.

We have considered as mixed depressive states also the cases without motor agitation but with intense psychic agitation. In a previous paper (6), we have discussed this issue. Many Authors have expressed the same view. Kraepelin (7) states: 'Sometimes it is more 'inward anxiety and trembling', a painful tension…sometimes it is an anxious restlessness, which finds an outlet in the most varied gestures, in states of violent excitement, and in heedless attempts at suicide. These moods are most frequently found in the periods of transition between states of depression and mania; they are, therefore, probably most correctly regarded as mixed states of depression and manic excitability'.

There is a fundamental psychopathological problem in the issue of mixed or agitated depression: namely, that excitatory processes may cause psychic pain, anxiety, suicidal ideas, anhedonia, inability to function and other symptoms which are usually associated with and caused by depression.

A century and a half ago W. Griesinger (8) had this intuition without the help of modern psychopharmacology:

> By using the expression 'psychic depressive states' we did not mean to imply that the basic nature of these states is inactivity and weakness and suppression (depression) of the psychic or cerebral processes that underlie them. We have much more reason to assume that very intense states of irritation of the brain and excitation of the psychic processes are very often the cause of such states; but the end result of these (psychic and cerebral) states as far as mood is concerned is a state of depression or of psychic pain. (Griesinger, 1861)

## Mixed affective states and agitated depression

From classical antiquity to the end of the 19th century, melancholia was described in various forms, many of which would today be considered mixed affective states.

The nosologists of the 18th century, such as de Sauvages (9) and Cullen (10) classified among the melancholias such forms as *melancholia phrontis*, *melancholia moria*, *melancholia saltans*, *melancholia errabunda*, *melancholia silvestris*, *melancholia furens*, *melancholia activa*, *melancholia excitata*, *melancholia delirans*, *melancholia persecutionis*, *melancholia convulsiva*, *melancholia maniaca*, *melancholia malevolens*, *melancholia homicidialis*, *melancholia metamorphosis*, *melancholia uterina*, *lycanthropia* and *melancholia enthusiastica*. Lorry (11) described *mania melancholica* and Guislain (12) *melancholie maniaque*. These names, even taking into account the nosologic imprecision of the time, clearly show the excited-agitated nature of these forms of depression. Heinroth (13), Griesinger (14), Falret (15), Kahlbaum (16) and many others described mixed

depressive states. Richarz (17) coined the name of *melancholia agitans*.

The nosographic evolution during the 19th century led eventually to the creation of *manic-depressive insanity* by Kraepelin in 1899 (18) and the definitive substitution of the term of melancholia with that of depression.

Kraepelin was the first to describe systematically the mixed affective states. He made them the cornerstone of the manic-depressive entity. In conceiving the manic-depressive entity, Kraepelin started from the excitement or depression of the three domains of psychic life: the intellect (train of thought rather than its content), mood, and volition (expressed in psychomotor activity).

Kraepelin described two syndromes of mixed depression: *depression with flight of ideas* and *anxious* (*agitated*) *depression*. The difference between these two syndromes is the presence of flight of ideas in the first and inhibition of thinking in the second.

In 1899, a monograph appeared on *Mixed States of Manic-Depressive Insanity* by Kraepelin's pupil Weygandt (1), based on a study carried out in Heidelberg. He focused only on three types of mixed state: *manic stupor*, *unproductive mania*, and *agitated depression* (*agitirte Depression*) with depressed mood, psychomotor excitement and inhibition of though or flight of ideas. This is the first time to the authors' knowledge that the term *agitated depression* was used. Weygandt pointed out the similarity with agitated forms of *involutional melancholia* and, similar to Lange (19),

Specht (20), Thalbitzer (21) and Bumke (22) considered *melancholia agitata* a mixed state of manic-depressive insanity, in contrast to Wernicke's (23) school of thought, which viewed it as a form of anxiety psychosis.

Interest in mixed states was waning by the 1920s. In 1923, Jaspers (24) wrote that the issue of mixed states 'did not have any further development, and this was very natural since elements of understanding psychology had been considered as objective components and factors of psychic life'. Schneider (25) was more hasty: 'We no longer believe in manic-depressive mixed states. Anyway, what may look like this is a change or a switch, if it pertains to Cyclothymia at all.'

On purely psychopathologic grounds, without any knowledge of the underlying neuropathologic alterations, it is difficult to make significant progress in this field. The present interest in mixed states is due to the adverse effects of antidepressants and the beneficial effects of lithium, anticonvulsant mood stabilizers, neuroleptics and atypical antipsychotics.

At present, agitated depression has lost its status as a mixed state, not only in the DSM system, but also in the view of most psychiatrists worldwide. Thanks to the widespread use of antidepressants coupled with the diminishing use of ECT, the different response of agitated and psychotic depression has become increasingly clear. *Agitated depression* was considered a subtype of *major depressive disorder* in the *Research Diagnostic Criteria* (RDC) (2) but was not carried over in the DSM-III-R (26) or the DSM-IV (27).

Thus, MDE with or without agitation are treated in the same way. The result is disastrous in many cases of agitated depression: both symptoms and course worsen.

In recent years, a growing number of psychiatrists (3, 6, 28–35) have expressed disenchantment with the official view, proposing agitated depression as a mixed form of affective disorders. The DSM system opposes this view because agitated depressives do not simultaneously meet the criteria for mania and major depression. This 'full mixed state' occurs rarely.

### Clinical picture of agitated depression

Depressed, anxious mood and inner, psychic agitation dominate the clinical picture of agitated depression. Psychomotor agitation is present in many cases, but not in all. In the cases without psychomotor agitation, inner unrest is the main symptom. This inner agitation makes the patient very anxious and fearful. They describe it as intense inner tension and use metaphors such as 'I feel like I'm bursting inside,' or 'I feel a violent force inside me as if I wanted to smash everything,' or 'I feel there are blades tearing through my guts.' They describe an internal shaking or an electrical current passing through the body. This tension is also manifested as muscular tension or pains. Diastolic blood pressure is found typically increased to 90 or 100 mmHg. The inner unrest manifests itself also with irritability or feelings of unprovoked rage. The patient just complains about it. In other cases, there is irritability and, at times, verbal and rarely physical violence, usually within the family environment as noted by Lange (19). In extreme cases, this rage combined with hopelessness is the cause of the violent character of suicide attempts, of which *raptus melancholicus* is the utmost example. At least some suicide–homicide cases are due to agitated depression. The difference from manic aggressiveness is that in manic patients anger is provoked by some external cause and is directed outward.

Many patients suffering from agitated depression complain of a disturbance of the train of

thought that they call *crowded or racing thoughts* or other similar names. These rapid thoughts are not expressed verbally by the patients. They are tormented by them. The flight of ideas in manic patients is expressed verbally in an abundance of words or pressured or clearly logorrheic speech.

Richarz (17) also observed that in mania thoughts tend to form strings of ideas (*Reihenbildung von Vorstellungen*) that link together by their content, alliteration, or assonance. In racing thoughts, the ideas come and go rapidly as if they were hunting each other or continuously overlapping without any link between them. Depressive ruminations are different. They consist only of a few thoughts that carry the anxieties and fears of the patient, and they are constantly present or recur frequently. The patient complains of their content but not of their course. There are naturally cases of transition between crowded thoughts and ruminations and making the distinction may be difficult.

An interesting split is often observed between motor agitation and racing or crowded thoughts. Their relationship appears to be inversely proportional. Mental excitement is more frequent and more intense in patients who do not show marked motor agitation. There is a striking analogy with manic states, in which the presence of delusional ideas is inversely proportional to psychomotor excitement. This phenomenon may have played a decisive role in the success of political and religious fanatics who created a vast popular following. It can be assumed that if their delusional or semidelusional ideas had been accompanied by patent motor excitement, they would not have had the same charismatic influence on their audience.

The speech of the patients with mixed depression fails to show any sign of inhibition. It is abundant and, in some cases, tends to resemble the pressure speech of manic patients.

The suffering of these patients must be very intense and often unbearable and is the main cause of suicide. Because of the great energy and impulsivity characteristic of agitated depression, the risk of suicide is very high. 'I wanted to kill myself to stop my agitation' a patient said. Sometimes they inflict themselves a physical pain to cover the psychic pain. This psychic pain is expressed in a dramatic way and, especially in women; they may be interpreted as hysterical manifestations.

Lability of mood and emotional reactivity is also characteristic of the clinical picture of agitated depression.

In contrast to the absence of retardation in speech and movement, there is an inhibition of purposeful activity, which in the more severe cases is nearly complete. In mild forms, the patient is quite active and sometimes anxiously hyperactive. Anhedonia and lack of interest are marked in all cases. Early insomnia, often sustained by racing thoughts, is common (36).

### Clinical forms of agitated depression

The following clinical forms can be distinguished:

*Psychotic agitated depression*: these patients present with depressed mood, restlessness, anxiety, delusions of guilt and persecution, hypochondriacal ideas and, often, strong suicidal impulses. The similarity of this syndrome with that of other psychotic depressions that do not present with motor agitation is notable (37, 38). In the latter, the patient lies silently in bed. On questioning, the patient describes an intense inner agitation, often located in the chest, abdomen, or head. A young patient said he felt 'blades ripping through his guts'. Some patients describe racing or crowded thoughts.

*Agitated depression (non-psychotic) with psychomotor agitation*: patients do not present delusions or hallucinations. The picture is dominated by depression, anxiety and motor agitation similar to that described in the RDC criteria (39). The patient may complain of crowded thoughts.

*Mixed Depression with psychic agitation*: the patient does not appear outwardly agitated, or the motor agitation is limited, but there is total lack of retardation. The patient speaks fluently and moves normally. The patient complains of intense inner agitation. The psychic pain of the patient is relentless, and the patient feels unable to perform normal tasks or enjoy anything. Frequently the patient complains of racing or crowded thoughts.

The term *Mixed Depression with psychic agitation* is replacing the term *excited anxious depression and the term Minor agitated depression* that we previously proposed (6, 36). This syndrome is similar to Kraepelin's (7) *depression with flight of ideas* and Lange's *excitable depression* (19).

### Diagnostic criteria of agitated depression

Full depressive syndrome and inner unrest are both essential elements of this syndrome. The presence of motor agitation is sufficient to make the diagnosis, as in the RDC criteria, because it also confirms the presence of psychic agitation. The absence of motor agitation creates the diagnostic problem of distinguishing anxiety from the particular inner unrest of agitated depression. To clarify the differential diagnosis between anxiety and inner agitation, pending more systematically validated criteria, we used the following criteria: along with

*major depression* and *inner agitation*, at least three of the following symptoms must be present: i) *Racing or crowded thoughts*, ii) *irritability or unprovoked feelings of rage*, iii) *absence of signs of retardation*, iv) *talkativeness*, v) *dramatic descriptions of suffering or frequent spells of weeping*, vii) *mood lability and marked emotional reactivity* and viii) *early insomnia*. Such symptoms are of excitatory, not depressive, nature and indicate the absence of inhibition.

## Material and methods

In the present study, we examine all BP and UP patients seen and treated at the Centro Lucio Bini in Rome from January 1999 to June 2006. These patients were diagnosed according to DSM-IV criteria except for agitated depression with motor agitation, where the RDC were applied and for agitated depression without motor agitation where our diagnostic criteria described above were applied.

Clinical information was collected directly from the patients, from the family members and from available medical records.

## Results

### Spontaneous and induced agitated depression

The total population of psychiatric patients was 2141 (women 1157 (54%), men 984). Table 1 shows the nosologic diagnoses of the patients affected by mood disorders:

One thousand and twenty-six patients presented with a MDE. Table 2 shows the nosologic diagnoses of these patients according to the distinction in BP I, BP II, UP depression and first episode of major depression:

Of these 1026 MDE, 346 (33%) were classified as mixed depressions (women 237, men 108). One hundred and seventy (49%) of them presented psychic and motor agitation and were diagnosed as agitated depression according to the RDC criteria.

Table 1. Mood disorders treated at Centro Lucio Bini of Rome (1999–2006)

| | Female | Male |
|---|---|---|
| BP I | 247 | 182 |
| UP mania | 12 | 12 |
| First mania | 6 | 9 |
| BP II | 260 | 183 |
| Cyclothymic D | 95 | 55 |
| UP | 232 | 155 |
| First MDE | 71 | 48 |
| Dysthymic D | 4 | 22 |
| Total | 927 (58%) | 666 |

BP, bipolar; UP, unipolar; MDE, major depressive episode.

Table 2. Major depressive episode according to the patient nosologic diagnosis

| | |
|---|---|
| BP I | 136 |
| BP II | 417 |
| Unipolar | 355 |
| First Dep | 118 |
| Total | 1026 |

The other 176 suffered of major depression with psychic agitation, according to the criteria exposed above.

Table 3 shows the nosologic diagnoses of the patients that presented the clinical picture of agitated/mixed depression, considering together depressions with motor and psychic agitation and depression with only psychic agitation.

Of the 346 patients with mixed depressions, 35 were excluded because they were alcohol or drug abusers. Of the remaining 311 mixed depressions, 138 (44%) were spontaneous, i.e. the agitation was present from the beginning of the episode or set on independently from pharmacologic treatments. In the other 173 (56%) patients, the onset of the agitation, either psychic or motor one, was associated with pharmacological treatments, mainly antidepressants (see Table 4).

The onset of agitated depression took place either immediately or within a few days to a few weeks. The great majority of agitated depressions emerged during treatment with Serotoninergic Selective Reuptake Inhibitor (SSRI's) (134 cases), tricyclic antidepressants (TCA) (49 cases), other antidepressants (16 cases), interferon (two cases) and withdrawal of an antimanic treatment (three cases).

It may be of interest that motor agitation was present in 30% of spontaneous cases and in 68% of induced ones.

If we compare the number of induced mixed depressions to the number of MDE separately for each nosologic group, we find that 33 belonged to BP-I patients (24% of all depressions of BP-I patients), 78 belonged to BP-II (19%), 50 were UP

Table 3. Mixed depressions according to the patient nosologic diagnosis

| | |
|---|---|
| BP I | 69 |
| BP II | 132 |
| Unipolar | 106 |
| First Dep | 39 |
| Total | 346 |

Table 4. Agents associated with the onset of mixed depression

| | |
|---|---|
| SSRI's | 134 |
| TCA | 49 |
| Other antidepressants | 16 |
| Interferon | 2 |
| Antimanic agents withdrawal | 3 |

(14%) and 12 (10%) were at their first affective episode.

One hundred and twenty-seven women (53% of all women with agitated depression and 20% of all women with MDE) and 46 men (42% of all men with agitated depression and 11% of all men with MDE) became agitated in association with the above mentioned treatments.

Among our 346 agitated depressions, 41 (28 women and 13 men) also had psychotic symptoms. As psychotic symptoms we considered hallucinations, delusions, both congruent and non-congruent (true delusions and not mere fears or doubts), and the presence of a state of mental confusion and grossly disturbed behaviour. Of these patients, nine (22%) were spontaneous, i.e. the psychotic symptoms emerged spontaneously. In the other 32 patients, the psychotic symptoms emerged in association with antidepressant treatment.

Another group of 27 psychotic depressive patients did not fully meet the criteria of agitated depression. Our clinical impression, however, is that psychotic symptoms in depression emerge out of a mixed affective state.

## Discussion

### Latent agitated depression and the issue of antidepressant-induced suicidality

As described above, there are many cases of depression that, though without manifest psychic or motor agitation and without psychosis, rapidly become agitated after the institution of antidepressant drug treatment. All antidepressants can induce this effect in certain patients but in our clinical experience the most rapid triggering is seen with SSRIs. Probably the cases of suicidal or other violent acts attributed to SSRIs and other antidepressants in recent years may be due to the agitation induced by the drugs in patients who were already agitated or prone to agitation. Reading the clinical descriptions of these cases, it is clear that the suicidal ideas have emerged from a state of agitated depression (40, 41), the psychomotor component of which is often seen as akathisia (42, 43). Clinicians often consider the emergence of agitation as an adverse reaction, but it is clearly the emergence of a new syndrome, just as in the case of antidepressant-induced mania. This modification of the depressive syndrome is of great concern not only for its inherent risks, but also given the fact that it is iatrogenic.

We propose the term *latent agitated depression* for these depressions prone to agitation. How can they be identified or at least suspected? According to our observations, the most reliable signs are:

i) total lack of inhibition in speech and movement;
ii) a certain mental vivacity unusual to inhibited depression;
iii) rich description of their depressive suffering;
iv) early or middle insomnia rather than late insomnia.

These signs are not of absolute value but may suffice to suspect a latent agitated depression and make the clinician more cautious with treatment.

### Treatment of agitated depression

Many authors have reported the beneficial effect of typical antipsychotics (3, 4, 44, 45), atypical antipsychotics (46, 47), anticonvulsants (48), and benzodiazepines (49). The rapid and effective action of olanzapine should be underlined (36, 50).

Parker (51) advances the hypothesis that atypical antipsychotics may have antidepressant effect, particularly in treatment-resistant melancholic depression, and suggests the term *atypical antidepressants*. We maintain, as explained above, that the antidepressant effect is due to the antimanic action of these agents in cases of depression of a mixed nature.

The best results are obtained by initiating treatment with antipsychotics, benzodiazepines, anticonvulsants or lithium. Perhaps the most rapid effect is achieved by a combination of antipsychotics and benzodiazepines. Haloperidol and clonazepam are equally effective. In cases of *mixed depression*, with only psychic agitation, even lower doses of haloperidol and clonazepam, such as 2 mg, may be effective in as little as 48 h. In more resistant cases, higher doses are required. ECT is rapidly effective and should be a first choice treatment in severe cases.

The main problem of the *mixed depressive states* lies in the term *depression*. Clinicians and laypersons automatically relate such a state of depressed mood to lower activity of the nervous system, as Cullen did, and physicians today prescribe antidepressants to most patients who look and behave depressed, just as they prescribe antimanic medication for those who behave in an excited way. But there is an important clinical evidence that excitatory brain processes may cause, as Griesinger states, despondent mood, anxiety, and symptoms of inhibition like in stages II and III of mania, as described by Carlson and Goodwin (52).

Flight of ideas, racing thoughts, and crowded thoughts are clearly excitatory phenomena. Neuronal hyperactivity must underlie them. This hyperactivity is dramatically confirmed by the effect of antidepressant medication. The thoughts are

further accelerated and intensified; the patient becomes exasperated to such a point that sometimes he or she wants to commit suicide.

There is certainly great similarity between depressive anxiety and the psychic agitation characteristic of agitated depression. Anxiety in typical depression is an emotional reaction to the painful experience of the depression itself. Human beings react with anxiety to stress factors of much lesser entity. This anxiety improves with antidepressant medication. Often, it is the first symptom to disappear. The anxiety observed in agitated depression is inherent in the agitation itself. The anxiety present in agitated depression appears to be a form of excitation or arousal. Patients of considerable introspective capacity describe this inner agitation as a great energy that strikes and possesses their minds and sometimes their bodies too, in a way that annihilates their capacity to think, feel, concentrate, or do anything. Racing thoughts have the same annihilating effect, probably because they are conveyed by this abnormal energy. The total inactivity, the despair, the undirected and groundless rage, and the violent suicidal impulses, all the essential elements of classic melancholia and of the more mundane agitated depression of today, seem to be caused by that ominous, dark force. This force is so violent that it cannot be anything but manic in nature.

These patients fully meet the DSM-IV criteria for major depression. The patients with Mixed Depression presenting only psychic agitation do not meet the RDC criteria for agitated depression because of the absence of psychomotor agitation, and they do not meet the criteria for a DSM-IV mixed affective episode because of the absence of a clear manic syndrome. Yet this form should be considered as a mixed state not only for the racing thoughts, that are undoubtedly a sign of excitation, for the irritability, and for the emotional lability, but also for the course of this disorder and the reaction to antidepressant treatment. Because of the lack of inhibition and because of the intense expression of their suffering, these patients are often diagnosed as presenting reactive or personality disorders.

In the variety of depressive syndromes that are included under the label of MDE, agitated or mixed depression is of particular importance because of its response to treatments. This response is radically different from that of the simple depression. Classifying it as a distinct syndrome and treating it adequately, will improve substantially the therapeutic outcome.

Specht (20) considered agitation and flight of ideas as manic elements and melancholia agitata and *agitated depression* as mixed manic-depressive states. He made the same assessment of melancholic delusions and proposed classifying every mixed state with depressive mood as melancholia.

We think that the old term *Melancholia* should be reinstated in modern nosology and be included in the Axis I diagnoses of the DSM system. It should include all depressive syndromes characterized by the 'melancholic features' of depressed mood, psychomotor retardation, anhedonia, circadian variations and vegetative symptoms. This form of depression is particularly responsive to ECT and fairly responsive to TCA.

The forms of melancholia without retardation but with motor or psychic agitation could be named *Melancholia Agitata*. The great difference in the treatment response warrants this distinction. They respond well to ECT, antipsychotics and mood stabilizers but deteriorate with antidepressants, especially SSRI's. Today this form of depression is usually called Mixed Depression or Agitated Depression. These names reflect well the mixed nature of these syndromes. Certainly, the name Melancholia fits better the psychotic forms.

The names *Melancholia* and *Melancholia Agitata* not only represent a great psychiatric tradition, but also fully convey the tragic human experience of these patients and bear out a deeply significant fact: the major psychiatric syndromes have remained unchanged over the course of thousands of years. If they are not disease entities, they surely are what Falret (53) used to call *formes naturelles*.

Both the above forms of Melancholia can present psychotic symptoms.

The other depressive forms of the heterogeneous entity *Major Depression* could be called *Non-melancholic depressions* until new clinical or neurobiological data will allow their better classification.

This nosologic proposal is based on wide clinical observations and data. Its application could lead to a better outcome and a shorter therapeutic delay of melancholic patients and it would avoid the therapeutic hazards of the agitated forms when treated as major depressions.

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