The primacy of mania: A reconsideration of mood disorders

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Abstract
In contemporary psychiatry, depression and mania are conceived as different entities. They may occur together, as in bipolar disorder, or they may occur separately, as in unipolar depression. This view is partly based on a narrow definition of mania and a rather broad definition of depression. Generally, depression is seen as more prominent, common, and problematic; while mania appears uncommon and treatment-responsive. We suggest a reversal: mania viewed broadly, not as simply episodic euphoria plus hyperactivity, but a wide range of excitatory behaviors; and depression seen more narrowly. Further, using pharmacological and clinical evidence, and in contrast to previous theories of mania interpreted as a flight from depression, we propose the primacy of mania hypothesis (PM): depression is a consequence of the excitatory processes of mania. If correct, current treatment of depressive illness needs revision. Rather than directly lifting mood with antidepressants, the aim would be to suppress manic-like excitation, with depression being secondarily prevented. Potential objections to, and empirical tests of, the PM hypothesis are discussed.

Keywords: Bipolar disorder; Mania; Depression; Prophylaxis; Antidepressants; Lithium; Antipsychotics; Mood stabilizers; ECT; Suicide

1. Introduction

In contemporary psychiatry, depression and mania are conceived as different entities. They may occur together, as in
bipolar disorder, or they may occur separately, as in unipolar depression. This view is

partly based on a narrow definition of
mania (the occurrence of euphoric or irritable mood with hyperactivity, decreased need for sleep, and a few other symptoms, occurring episodically for 1 week or longer) and a rather broad definition of depression (episodes are denned as depressed mood with changes in sleep, appetite , interest, or energy lasting for 2 weeks or longer; chronic depression is captured in the definition of dysthymia). In epidemiological studies and in clinical practice, depression is seen as more prominent, common, and problematic. Mania is viewed as uncommon and easier to treat. In this paper, we suggest that the concepts should be reversed: mania should be viewed quite broadly, not as simply episodic euphoria plus hyperactivity, but as reflective of a wide range of excitatory behaviors; depression should be seen more narrowly.Further, we hypothesize that the two conditions are connected, and unidirectionally; again in contrast to previous theories of mania interpreted as a flight from depression, we propose the primacy of mania hypothesis (PM): depression is a consequence of the excitatory processes of mania.
Our proposition is new, and yet old . It is now because most psychiatrists have become so ingrained with our current narrow
definition of mania that they cannot imagine the validity of a broader connection to excitation. Yet it is old, because the term “mania” was used from ancient Greece until the 1960s to mean something much broader than how we conceive it now.
Which perspective is more correct , the old broad view or the current narrow view , is open to question and should be answered with research. Yet , to refuse to ask the question would mean assuming that the newer narrow view of mania is correct, or has been proven to be correct. As we will show in this paper , the presumption that our current definition of mania has disproven the older broader view is based on inadequate scientific or clinical evidence . In fact, we think the available evidence better supports the ancient view of mania as a synonym for mental and physical excitation, and a correspondingly narrower perspective on depression as its consequence.

2. Background

For over 2000 years, mania was considered the main form of mental illness [22,23], with leading clinicians such as Pinel
considering mania the most common form of mental illness [106], Heinroth seeing it as the “fundamental affection of the
psyche” [68], and Griesinger viewing excitatory phenomena as causative of some depressive states too [61]. Kraepelin,
carrying on this tradition, had broad criteria for mania: his many categories of mixed states and his fundamental states (temperaments) were basically conditions of excitement [84]. After Kraepelin, the clinical importance of mania diminished
and that of schizophrenia expanded [121], followed by the rise of psychoanalysis and the move towards diagnosis of unipolar
major depressive disorder in DSM-III[13,105,121]. The recent revival of interest in a broader spectrum of bipolar [1]

or mood [32,60] disorders has produced some confusion [38], partly because contemporary psychiatry has become
comfortable with the idea that depression is common, debilitating, and independent of mania [119,137]. Reversing this
emphasis, we discuss the converse possibility – that mania can be seen as the core psychopathology of mood disorders,
with depression its consequence.
In Rome, one of us (AK) has led a group of clinicians that has published observational data about the course of bipolar
disorder over four decades [79,81,83,87]. In this paper, we draw on that experience and on the psychopharmacology literature to re-examine the broad concept of mania as the prototype of nervous excitatory processes. We suggest the primacy of mania (PM) hypothesis: not only is there an intrinsic link between mania and depression, but also the excitatory process of mania is the primary process, with depression being a secondary result. Metaphorically speaking, mania is the fire and depression its ash . In the first part of this paper, we provide background for the PM hypothesis from two main sources: pharmacotherapy and clinical psychopathology (Table 1); in the second part we consider some objections to
the PM , followed by a discussion of clinical implications if the PM hypothesis is correct.

Table 1
Evidence for the primacy of mania hypothesis

Clinical psychopharmacology
1. Lithium prophylaxis
2. Lithium discontinuation
3. Limited direct benefit for depressive symptoms with lithium, anticonvulsants, or antipsychotics
4. Antidepressant-induced mania or rapid-cycling

Clinical psychopathology
1. The mania-depression-interval (MDI) cycle pattern
2. Mixed states
3. The subjective experience of patients

3. Evidence from clinical psychopharmacology

3.1. Lithium prophylaxis and discontinuation

The first observations that gave rise to the idea of the primacy of mania came from the course of manic-depressive recurrences during continuous lithium treatment. As an anti-manic agent , lithium attracted little initial attention, partly due

to the perceived narrow diagnostic range of its usefulness , i.e.,mania.[120]. While testing the prophylactic action of lithium
against manic recurrences, some investigators also observed a prophylactic action against depressive recurrences [66].Schou fully understood the importance of these clinical observations, and performed with Baastrup the ground-breaking studies that established the prophylactic action of lithium against all the manifestations of manic-depressive illness [15,16]. The prevention of depression by an antimanic agent came as a surprise (which would occur again with antiepileptics and antipsychotics). The presumed explanation was that lithium prevented depression through an antidepressant action , just as it prevented manic attacks through its proven antimanic action. Yet a direct acute antidepressant effect of lithium has been less well-established [43,100] than the stronger evidence for its preventive effects on depression and mania (mood cycles)[26,35,60]. Indeed, one of us (AK) reported that lithium at higher serum concentrations (around 1.0 mEq/L) may prolong the duration of a depressive episode[87]. It is the case that acute antidepressant efficacy with lithium augmentation has been suggested in some studies of treatment-resistant depression [17]. Yet most of those studies were conducted before DSM-IV , thus potentially including persons with type II bipolar disorder, a phenomenon documented by a number of pre-DSM-IV antidepressant clinical trials [11,12,104]. Post-DSM-IV studies, particularly STAR-D,have not found much acute antidepressant benefit with lithium [42,43,100]. A recent meta-analysis which finds that lithium prevents mania more robustly than depression [45] does not entail the false conclusion that lithium does not prevent depression; indeed it has a notable effect size for such depression prevention benefit relative to placebo.
The Rome group found that if lithium did not suppress manic phases,then the depressive episodes that followed remained
unchanged [86]. However,if lithium attenuated manic episodes,the following depressive episodes also were shortened. When
mania was completely prevented, depression did not occur [86].In the following years, the Rome group observed that patients
with cycles that begin with mania have a better response to prophylactic lithium than those with cycles that begin with
depression followed by mania/hypomania [88]. This observation has been subsequently replicated [62]. While the most common explanation [62] for this observation is that there may be a specific subtype of bipolar disorder, characterized by the MDI course,which responds preferentially to lithium, an alternative explanation could be that lithium more effectively prevents manic processes, thus averting subsequent depressive episodes.
Further evidence forthe potentialimportance of antimanic action in prophylaxis stems from lithium discontinuation studies. Numerous groups have confirmed that abrupt lithium discontinuation leads to manic, rather than depressive, relapse [82]. These observations strongly suggest that mania is a lithium discontinuation rebound phenomenon; it would be logical to surmise that if the rebound takes the form of mania, then the therapeutic action exerted was an antimanic one.

3.2. Anticonvulsants

As with lithium, the antimanic effect of antiepileptics was discovered first, and only subsequently was a prophylactic effect against both mania and depression revealed. Despite the general belief that at least some anticonvulsants, like lamotrigine, have acute antidepressant effects, the evidence for acute antidepressant efficacy [27], as opposed to prophylactic benefits
[24,28],is weak. In the case of lamotrigine, multiple unpublished studies find no benefit with this agent in either unipolar or bipolar acute depression [29]. While alternative explanations exist other than lack of efficacy (such as the inability to show
benefit in 8-week studies due to the slow dosing titration of lamotrigine),it remains the case that lamotrigine has repeatedly
failed to prove effective in acute bipolar depression.
Instead it seems clear that lamotrigine has robust prophyactic properties, better than placebo for both mania and depression in pooled analyses (though relatively more so for depression than for mania)[58]. As with lithium, the long-term benefit seen with lamotrigine for depressive episodes might be related to prophylactic effects rather than direct antidepressant effects. This disconnect between acute and prophylactic efficacy is hard to reconcile with the received wisdom that equates benefit for depression with acute antidepressant efficacy. Yet it is consistent with the PM hypothesis. Prophylaxis of depressive episodes may be sui generis, separate from acute efficacy, and not related to specific prevention of acute depression as opposed to acute mania;instead, if a drug is to prevent depressive episodes, perhaps it may need to prevent both mania and depression, or else it will prevent nothing at all.

3.3. Antipsychotics

With atypical antipsychotics, the standard pattern holds: efficacy in mania was first demonstrated, followed by use in prophylaxis. Antidepressant effects have also been attributed to these agents (especially olanzapine/fluoxetine combination
and quetiapine)[30,129], and the term ‘atypical antidepressant’ has been proposed [103], but this evidence, once again, is
weaker than the evidence for antimanic efficacy. Numerous studies with olanzapine eitherfind no acute antidepressant
benefit in monotherapy [114,127], or a small effect size of benefit [129]; the antidepressant efficacy of olanzapine-fluoxetine combination may be due more to the fluoxetine,than the olanzapine, component[25,127,129]. Even the recent quetiapine data are not clearly representative of benefit for pure depression. Rather, given the extremely narrow DSM-IV definition of mixed episodes and the corresponding broad criteria for major depression, itis possible that such “antidepressant” benefit in factreflects the presence of some mixed/agitated symptoms [80]. Mixed/agitated depressions,subthreshold for full DSM-IV mixed state criteria, can be characterized by motor agitation and/or psychic agitation manifested by lack of inhibition,intense innertension,racing thoughts, unprovoked

anger,talkativeness, early insomnia, mood lability, dramatic suffering and psychic pain [20,80]. In addition to the presence of excitatory symptoms,the course of mixed states differs from pure depressive episodes in that about 30% are followed by depression while hypomanic switch is rare [78]. Further, unlike pure depression, antidepressants often worsen agitation and manic symptoms in depressive mixed states [55].
The prevalence of agitated/mixed depressive syndromes among major depressive episodes is not negligible,ranging from 19 to 44% of unipolar or bipolar depressive episodes [124].If this is true, then this prevalence is important for clinical trials of major depression:the presence of such depressive mixed states may explain some of the benefits seen with antipsychotics as well as impede potential benefits of antidepressants for pure depression.
In fact, the observation of apparent antidepressant benefit with antipsychotics is not new and perhaps not even specific to
atypical antipsychotics. In a review of 34 RCTs of traditional antipsychotics versus tricyclic antidepressants or placebo,
typical antipsychotics generally showed benefit for “mixed anxiety@depressive states” [113]. It is possible that much of
the apparent benefit of antipsychotics for depressive syndromes may be related to the presence of some concomitant manic symptoms. Whether such antipsychotics are effective in pure depression, in the absence of any manic symptoms, has not been studied.

3.4. Antidepressant-related mania or rapid cycling

Without doubt the role of antidepressants is the most controversial matter in the clinical treatment of bipolar disorder. We do not intend to provide complete and convincing discussion here of the pros and cons of antidepressants in bipolar disorder, which we have discussed extensively elsewhere [51]. In sum,it appears that the following conclusions may be inferred from the available randomized clinical trials (RCTs): first, although antidepressants have been shown to be effective compared to no treatment (placebo alone) or an antipsychotic (olanzapine) in a recent meta-analysis of acute efficacy [54], antidepressants have still not been shown to be more effective than therapeutic levels of lithium or other mood stabilizers for treatment of the acute major depressive episode[99], including the largest study of the topic,recently published in the NIMH-sponsored STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder) study [116].Second, although the same meta-analysis found no evidence of antidepressant-induced mania in placebo-controlled studies, such evidence in fact exists with tricyclic antidepressants (TCAs) compared to other agents [54]. Third,repeated RCTs demonstrate lack of efficacy of antidepressants, both TCAs and newer agents like serotonin reuptake inhibitors (SRIs),in prevention of mood episodes in bipolar disorder[47,50]. The presence of observational data to the contrary [9.lo,36,72], as well as corroborating [14,48,52,53,81],the randomized findings should be interpreted in light of basic principles of evidence-based medicine,i.e.,that randomized data, where available,

are more valid than observational data [117]. Fourth,in the only two studies designed to assess the issue [49,134],randomized data exist that antidepressants are associated with rapid cycling and more depression in rapid cyclers, and there are no contrary randomized data from studies designed to examine the topic (as opposed to post-hoc analyses whose positive [111] or negative [108,109] results are prone to chance or lack of statistical power).

Thus, we believe that an objective reading of the scientific literature throws the efficacy and safety of antidepressants in
bipolar disorder into some doubt.

A clinical experience that we have not yet seen studied in research settings may explain some of the divergent views
regarding antidepressants [51,92,93].In the observational experience of the Rome group,it appears to be easier to maintain prophylaxis with the use of mood stabilizers during the inter-episodic free interval, or at the beginning of a period of excitement. However, the use of the same mood stabilizers appears to be much less effective during the acute major depressive episode. This is usually interpreted as lack of acute antidepressant effect for mood stabilizers; another possibility,
related to the PM hypothesis,is that depression is more easily treated indirectly, by first preventing or treating the manic
phase, rather than directly during the depressive phase.

Hence,the corollary to cautious use of antidepressants is not necessarily that mood stabilizers should be aggressively used in the acutely depressed bipolar patient. Rather,the Rome approach is, during the acute major depressive episode,to first diminish the dose of the mood stabilizer, which often results in depressive relief; then,if depression persists, add antidepressants. The key, however,is that once the acute phase is over,antidepressants should usually be stopped and mood stabilizer doses increased.In the most difficult cases,the Rome group actively uses ECT to treat the acute major depressive episode, and when the patient reaches euthymia,then aggressive treatment with mood stabilizers is again initiated. These
preliminary observations await empirical study to be confirmed or refuted.

In this perspective,the euthymic period is like Archimedes' lever of the world; if we can obtain it, we are much more able to
then engage in effective mood stabilizer prophylaxis. However,most clinicians only focus on treating the acute mood episodes,
and when euthymia is achieved,they simply continue antidepressants and often even decrease mood stabilizer use,thereby
minimizing chances of effective long-term prophylaxis.

4. Evidence from clinical psychopathology

4.1. Mania-depression-interval cycle (MDI) pattern

As noted above,the course pattern of MDIis associated with better treatment response than the DMI pattern [60,88]. This observation is explainable by the PM hypothesis: Manic episodes, even those with very acute onset, are preceded for days to weeks by prodromal excitatory symptoms, which lithium or other mood stabilizers can often easily control.

4.2.Mixed states

Also as noted above, mixed states are characteristic examples of the relevance of the PM hypothesis.If viewed broadly, so as to include both dysphoric mania [91,126] and agitated depressive states with one or more other manic symptoms (such as flight of ideas, also called “depressive mixed states”)[20,80],the empirical literature suggests that about one half or more of acute manic episodes [33], and up to one half of major depressive episodes [19], are varieties of mixed states. This phenomenology would indicate that pure mania and pure depression are both less common than mixed states. The frequent presence of excitation as part and parcel of depressive presentations is consistent with the PM hypothesis and hard to explain based on the classic bipolar/unipolar dichotomy [4,37].

4.3. The subjective experience of persons with bipolar disorder

Another source of evidence comes directly from bipolar patients and their relatives, which demonstrates the frequent pattern of depression following mania rather than vice versa. The literature on this point is vast. For example, Jamison wrote [70]: ‘it was difficult to give up the high flights of mind and mood, even though the depressions that inevitably followed nearly cost me my life.’In another example [34], a writer with bipolar disorder states that,’although I long for luminous ecstasies,I wouldn’t ask for any, because I know they are followed by great depressions.’

5. Potential objections to the primacy of mania

Since no conceptual review such as this can be entirely convincing to skeptics, we address next some potential objections to the PM hypothesis (Table 2).

Table 2
Potential objections to the primacy of mania hypothesis

1.The validity of unipolar depression
2.The depression-mania-interval(DMI) cycle pattern
3.The benefits of hypomania
4.Antidepressant-discontinuation related mania

5.1.Unipolar depression

Perhaps the main objection to the PM hypothesis is the existence and validity of unipolar depression, conceived as excluding any mania. At one level, unipolar depression may simply be a different disease than bipolar depression, with no link to excitatory phenomena. Alternative considerations may be relevant, however:first some unipolar depressive conditions occur in persons with hyperthymic temperaments (labeled as unipolar with hyperthymic temperament (U H-T)[31] or as type IV bipolar disorder[6]). Second, sometimes apparent unipolar depression is preceded by stressful life events [8,18,96] that cause subjective distress and sleep disturbance,with increased activity levels in the absence of other hypomanic symptoms. We propose that these periods, which may have a causal connection to subsequent depression, be termed hypomanic equivalents because of the emotional turmoil,hyperactivity, and reduction in sleep that often accompany them.In predisposed people,they can bring about the same nervous exhaustion/depression as true mania or hypomania.Third, many depressive episodes follow periods of intense anxiety or even panic,i.e., phenomena with intense nervous arousal. These types of depression,linked to anxiety-associated nervous excitement, could be seen as anxiety-associated depression [74,75,122]. Thus, at least from the perspective of a broad definition of manic-like symptoms,the concept of unipolar depression-unrelated to stressful circumstances or hypomanic equivalents, occurring outside of hyperthymic temperament, and unassociated with anxiety – would be much more limited than in the current heterogeneous DSM-IV definition. This perspective is supported by empirical research from Cassano and coworkers [32] who found that patients with currently defined recurrent DSM-IV unipolar depression endorsed experiencing a substantial number of manic/hypo-manic symptoms over their lifetimes.In both recurrent uni-polar depression and bipolarI disorder,the number of manic/hypomanic items endorsed was related to the number of depressive items endorsed, and predicted worse outcomes.This perspective of broad definition of manic-like symptoms is also supported by the notable prophylactic effect oflithium in recurrent unipolar depression,including benefit for mood episodes [60] and even for suicidality [64]in the unipolar population. Of course,the determination of which perspective is valid (a broad or narrow view of unipolar depression) depends on whether it is legitimate to use the term “mania” broadly, as did Kraepelin and as we suggest,rather than narrowly, as derived from Karl Leonhard [89] and DSM-III [121].

5.2. The depression-mania-interval(DMI) cycle

In about 25% of persons with bipolar disorder, depression is followed by hypomania or mania [88], an observation which would seem to contradict the PM hypothesis. Yet about 80% of patients with the DMI cycle sequence have type II bipolar disorder, about half with an excitable and labile temperament [88]. Further, about one-half of cases of bipolar disorder begin with depression as the first episode,rather than mania [60]. Yet such reports are usually based on retrospective recall, where it

has been shown that hypomania in particularis more often denied or forgotten [3], or that depressed individuals tend to
negatively recall their past,thus underestimating non-depressed periods [136]. Prospective studies of children are
needed, and many show depression to precede DSM-defined mania [46]. Yet anxiety and agitation are often prominent
[101], excitatory behaviors that we are including in our broader concept of mania. Often, depression in such patients is
not really the beginning of the cycle and does not come out of the blue, but rather depressive episodes are frequently
preceded by periods of temperamental instability [2,97,102],stress (including emotional excitation due to life events, both
positive and negative)[8,18,96], use of some stimulants like caffeine [133,135], and irregular sleep patterns [44,90]. We
would like to underline the fact that many of these hypomanias/manias that follow depression often emerge in association
with antidepressants [55,81].

5.3. The benefits of hypomania

Another potential critique might be that many patients simply have hyperthymic temperament(without any recurrent depressive episodes), or it might be argued that even if depression usually follows mania, hypomania is still often advantageous and productive. Patients enjoy these periods of exuberance [71]. Yet the line between harmful and fruitful hypomania – dark and sunny hypomania, Akiskal would say [5] – is not always clear; obviously,the benefits of hypomania (usually temporary) have to be weighed against the risks of depression (usually chronic). While we do not want to replace mild hypomania with mild chronic depression,the PM hypothesis,if true, would indicate that reduction in depression may require reduction in hypomanic excitement.

5.4. Discontinuation of antidepressants

While antidepressant-induced mania is plausible with the PM hypothesis, mania following discontinuation of antidepressants would seem to contradict it[57].It may be relevant that the former seems more common (with rates ranging up to 50% depending on the agent[56]), and is better documented, than the latter(reported to occur in about 5-10% of cases [7]).Other potential mechanisms,like anticholinergic rebound,for the infrequent occurrence of antidepressant-discontinuation related mania have also been suggested [41].

5.5. Empirical tests of the PM hypothesis

We do not want to leave the impression that the PM hypothesis can accommodate any critique, a claim seen by some as indicating that a theory is not scientific [107]. Rather,in agreement with the view that a scientific theory should make testable predictions, we suggest that the PM hypothesis can be tested by confirmation or refutation of the following empirical predictions, most of which can be (and have not yet been) examined in randomized clinical trial paradigms:

1. The interval between the end of a manic episode and the beginning of the next depressive episode should be shorter than the interval between the end of a depressive episode and the beginning of the next manic episode.

2. Prophylactic studies of mood stabilizers,like lithium or lamotrigine, would demonstrate more efficacy if these agents are started in a euthymic phase of treatment than if they are initiated during an acute manic episode.

3. Mood stabilizers will prove ineffective versus placebo in the treatment of pure major depressive episodes (without anxiety or any manic symptoms, and excluding persons with hyperthymic temperament); conversely, antidepressants will be effective in such conditions.

4. Antidepressants will prove ineffective in persons with depressive mixed states or in depression associated with hyperthymic temperament or hypomanic equivalents; conversely mood stabilizers or antimanic agents will prove effective in those conditions.

5. Mood stabilizers will prove effective, and more so than antidepressants,in the prophylaxis of unipolar as well as of bipolar depression.

6. Clinical implications

The idea that mania has primacy over depression sits uncomfortably in the context of current nosologies. From a purely practical standpoint, depression – which is more frequent, chronic, and difficult to treat than mania [73] – is,indeed,the major clinical problem in mood disorders. Yet if one views mania broadly (as the prototype of nervous excitement)related states like hypomania, mixed states, and hyperthymic, cyclothymic or irritable temperaments are also quite common.If these states give rise to depression,then the treatment of depressive morbidity would require more attention to these manic-like conditions.
Despite the continually expanding pharmacological options forthe treatment and prevention of depression,it is troubling
that our best recent studies,like the National Institute of Mental Health (NIMH) Sequenced Treatment Alternatives for Depression (STAR-D) study, demonstrate relatively limited remission rates, with only about one third of patients improving markedly even with

open-label acute treatment [132]. Long-term treatment based on sequenced alternatives overall found, once relapses at 1 yearfollow-up were included, only about 40% of patients with unipolar depression in remission with standard antidepressants [115]. These real-world; rates are much lower than most RCTs [94], and should raise a flag of concern [98].

The STAR-D results also provide some validation of observational and epidemiological findings that are not entirely reassuring. For instance,the literature on whether antidepressants cause or prevent suicidality is mixed [5,39,63,65,69,76,77], unlike the more consistent literature demonstrating suicide prevention benefits with lithium [59,128.130,131]. On the other hand,in some settings at least ecological data suggest that suicide rates are on the decline,correlative with increases in antidepressant use [63,77]. One can hope that there is a causal relation here, but countervailing studies leave some room for doubt[118].

Some of this conflicting experience may have to do with the practice of clinical psychopharmacology in a manner that is
inconsistent with the PM hypothesis; in this regard,the lack of recognition and adequate treatment of agitated depression as
a mixed state [80] may be a significant factor in many attempted or completed suicides [40]. Antidepressants can cause such mixed states [55,78], especially in persons with bipolar disorder who are misdiagnosed with unipolar depression. This factor in itself may explain the low but apparently real risk of suicide with antidepressants in children and some adults [21,112].

Further,in clinical practice,the observation of bipolar illnesses and mood cyclicity is on the rise, usually seen as due to increased attention to such matters on the part of clinicians [125]; but it has not been disproven that perhaps we are observing a real increase in mood disorder morbidity [85].

Itis easy to blame the antidepressant drugs [67], or the pharmaceutical industry that markets them [95], but perhaps part of the faultlays in how we clinicians use these drugs. As a great founder of psychopharmacology, Frank Ayd wisely advised, our advances in psychopharmacology and neuroscience have given us great tools which as clinicians we have perhaps not yet learned how to use, somewhat like being given a powerful automobile and a license to drive without sufficient experience in how to drive [138].If the PM hypothesis is correct, poor outcomes may result from lack of attention to preventing excitement in all its forms.

7. Limitations

We appreciate that this paper, being conceptual,is liable to many criticisms. The first, and perhaps most important,is that it is a selective review of the literature, and, with a selective review, one can uphold almost any idea. However, not all topics are amenable to a so-called systematic review of the literature, one which involves replicable examination of all available studies on a specific question, with inclusion and exclusion criteria. Sometimes, conceptual reviews are needed to get at basic

presumptions that are simply taken for granted in most of the literature, or for which an empirical database is sparse because researchers have not thought about the questions being asked. Readers in that case have only to rely on the notion that the authors do not have an axe to grind,that they are reporting what they think to be true, not simply what they wish to be true.

Second, many of our observations are untested; we intend this paper to be the raising of questions,rather than the answering of them; and a call for research into questions that have not been asked. Third, our theory is broad, and like most broad theories, can be adjusted to explain a wide variety of data; some data which seem to contradict the PM hypothesis are explained by extensions of the theory (such as the concept of hypomanic equivalents). We are aware that this approach is seen by some as the definition of a non-scientific theory [107].However,there is more than one philosophy of science [139]; and almost all general scientific theories can be adjusted to data [110]. When such adjustments are excessive or extreme, researchers often drop the theory in the face of recalcitrant data. But the mere fact of initially interpreting apparently contradictory data in the light of a theory supported by other data is not inherently unscientific.It is for further research and reassessment to determine whether a theory explains most of the data or not.

Fourth, some readers may dismiss the paper as speculative,or see it as having parts which seem to use evidence-based medicine (EBM)language about randomized clinical trials (RGTs), and other parts which seem anecdotal or based solely on clinical experience. Any potential critique on those grounds is based,in our view, on a mistaken understanding of EBM, not to mention medical science. EBM is not simply the adherence to RCTs, while ignoring experience and observational results. Rather,itis about a hierarchy of evidence,where higher levels of RCTs are seen as more valid, where available,than lower levels of observational data [123].However, observational evidence is evidence, and often valid;further,in the absence of RCTs,itis perfectly legitimate and scientifically sound to utilize available observational evidence [123]. We have taken that approach throughout this paper.

Fifth, one can be unconvinced by any single part of our interpretation of the literature. For instance, we suggested that the MDI course of bipolarillness,linked to lithium efficacy,supports the PM hypothesis. Some may argue that other explanations are also possible; perhaps some individuals simply respond to lithium, and they happen to have MDI patterns, while lithium non-responders happen to have other pattrns. This is true; we are not proposing that any single part of this analysis proves the PM hypothesis. We are suggesting that this entire literature, when viewed as a whole, seems more consistent with the PM hypothesis than with alternatives, and that , at the very least,research should be conducted to assess the

PM hypothesis rather than, as is currently the case, proceeding with other unanalyzed assumptions about the nature of depression and mania.

8. Summary

According to the foregoing hypothesis, depression would follow, and be a consequence of, states of prolonged nervous
arousal such as mania, hypomania, hypomanic equivalents,and anxiety. This hypothesis would support a parallelism between bipolar and unipolar depression. Continuous treatment with a mood stabilizer, as well as lifestyle changes designed to reduce stressors, may attenuate nervous arousal and by doing so, prevent the genesis of future depression.

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