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REVIEW ARTICLE

Is Mania the Hypertension of the Mood? Discussion of A Hypothesis

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Abstract: Beyond both being biphasic/bidirectional disorders (hypo)mania and essential hypertension share a surprising number of similarities and an overlap between their genetics, biological background, underlying personality and temperamental factors, precipitating factors, comorbidity and response to treatment, indicating a possibly partially shared biological background. Based on theoretical knowledge, similarities related to characteristics, manifestation and course, and the results of pharmacological studies related to the effects and side effects of pharmacotherapies used in the treatment of these two distinct disorders, the authors outline a hypothesis discussing the similar origins of these two phenomena and thus mania being the hypertension of mood in memory of Athanasios Koukopoulos, one of the greatest researchers and theoreticists of mania of all time.

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Keywords: Mania, bipolar disorder, hypertension, comorbidity, underlying mechanisms, temperament.

1. INTRODUCTION

Athanasios Koukopoulos (1931-2013), a brilliant Greek-Italian psychiatrist, an excellent clinician and original thinker introduced several avant-garde, pioneering ideas including the primacy of mania hypothesis in patients with bipolar (manic-depressive) mood disorder [1]. His way of thinking driven by clinical observations was original, suggestive and stimulating. Remembering him, we present here a hypothesis postulating that essential hypertension and (hypo)mania (which according to Koukopoulos is the primary component of bipolar disorder) may have a shared pathophysiology with similar biological, genetic and treatment response characteristics.

2. ESTABLISHING THE SIMILARITIES AND RELATIONSHIP BETWEEN CLINICALLY DIFFERENT DISORDERS

How can the etiological and pathophysiological identities and similarities between these two, clinically different disorders be detected and conceptualised? The classical disease-entity ("ens morbi") concept of Robert Virchow, the great German physician, at the end of 19th century postulates that similar or same a) genetics (heritability); b) cross-sectional clinical picture; c) course; d) end-stage; and e) autopsy findings put different illnesses into the same disease-entity category [2]. Of course, this concept has been developed for somatic/medical disorders, however, with some modifications it could be valid for psychiatric disorders as well.

In 1970 Robins and Guze [3] described five phases of establishing a valid classification of mental disorders: clinical description, laboratory study, exclusion of other disorders with similar symptoms, follow-up study (course), and family study. Later, the concept of external validating criteria for psychiatric illnesses have been developed and several criteria have been described including family history and genetic studies, age of onset, biological background (including biological markers), personality and temperamental factors, precipitating factors, illness course, treatment response, comorbidity and complications [4-6].

Out of these external validating criteria, treatment-response is a complex problem and needs further discussion. Considering our current, mainly descriptive nosology (clinical classifications, such as DSM-5 or ICD-10) treatment response is usually not specific; drugs with different modes of action can treat effectively the same disorder and one given drug could be effective in the treatment of different disorders. In several – but not all – cases the response to a given drug could be the reflexion of the fact that these different disorders have a common root or shared patho-physiology. For example, carbamazepine and some other anticonvulsants are effective in the treatment of epilepsy, trigeminal neuralgia and bipolar disorder [7] (the common characteristics of these disorders is their episodic (paroxysmal) course). Thus, regarding their clinical manifestations these are different illnesses but also possess some similarities, like episodic course, putting them in one big family of "paroxysmal,

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episodic/recurrent disorders". In this case, the beneficial effect of some antiepileptics in these three clinically different disorders might indicate that they have an at least partially shared biological background. In addition to the elevated comorbidity and shared treatment response between bipolar disorder and epilepsy a recent review suggested that the great overlap of several precipitating factors in mania and temporal lobe epilepsy imply that common brain processes may contribute to both superficially different disorders and this is indicative of shared pathophysiology [8]. Furthermore, bipolar disorder and epilepsy have further common characteristics, such as the kindling phenomenon which is recognisable in both cases [9].

On the other hand, treatment-response in several cases is not the reflexion of shared pathophysiology, particularly if the effect is related to different mechanisms of action of the given drug. Lithium, an effective antimanic and phase-prophylactic drug in the treatment of bipolar disorder has a specific antiaggressive/antisuicidal effect [10] but lithium was also successfully used in the treatment of hyper-thyroidism and leucopenia. Both of these latter effects are related to side-effects of lithium on the thyroid gland and haemopoiesis [11]. In these cases the similar efficacy in two different indications (hyperthyroidism and leucopenia) do not necessarily indicate a common biological background and therefore treatment response per se is not always a valid argument in researching and documenting a relationship between different disorders. Treatment response could be a useful external validating factor only if the mechanism of action is also similar/same in the two, successfully treated disorders. However, as we will see below, there are a lot of similarities and just a few differences between essential hypertension and mania.

3. SIMILARITIES AND DIFFERENCES BETWEEN ESSENTIAL HYPERTENSION AND MANIA (BIPOLAR DISORDER)

3.1. Familial-Genetic Studies

It is well-known that both mania and essential hyper-tension run in families; relatives of manic and hypertensive patients have a significantly higher lifetime risk for developing the same disease [7, 12]. Nevertheless, according to our knowledge, no studies on family history of hyper-tension in bipolar patients and family history of bipolar disorder in hypertensive patients were performed previously. However, studies using sophisticated genetic methods on data of the Wellcome Trust Case Control Consortium show that bipolar disorder and essential hypertension have some common genetic basis [13, 14].

3.2. Age of Onset

Mania (bipolar disorder) typically shows an early onset, particularly in the case of positive family history. On the contrary, the onset of essential hypertension is more common in middle age and in older persons, and its incidence increases with age. There is a natural tendency for blood pressure to rise with age even in non-hypertensive people [15]. However, the opposite is true for mania and bipolar disorder: the incidence and prevalence of manic episodes or manic component of bipolar disorder show a declining tendency with age while depressive episodes become more common in older persons [7]. At any rate, for both disorders, the earlier the onset, the worse is the clinical course and outcome.

3.3. Biological Background

3.3.1. Neurochemistry

Noradrenaline, dopamine and serotonin are strongly involved in the pathogenesis of both bipolar disorder and essential hypertension. Both manic episode and essential hypertension are characterised by overactivity of the central catecholaminergic (noradrenergic and dopaminergic) system**.** These abnormalities were discovered by psychiatrists and cardiologists in the second half of the last century independently of each other. An increased central sympathetic tone and abnormalities in dopamine/noradrenaline and serotonin production and receptor function have been described in human essential hypertension and rodent models of genetic hypertension as well as in bipolar disorder [7, 16-23]. As for serotonin, the name has come from the early belief in the 1950s that its main function is increasing the smooth muscle tone in vessel walls [20], later, however it was described that the role of serotonin in the regulation of blood pressure is not fundamental. On the other hand, serotonin – like noradrenaline and dopamine – also plays a significant role in the regulation of mood, cognition, anxiety, sleep, appetite, sexuality and aggression [24].

Catecholamines play an important role in the regulation of blood pressure which is supported *inter alia* by the fact that dopamine and to a lesser extent noradrenaline are the most widely used and also the most effective rapidly acting drugs to increase the pathologically low blood pressure [25]. If the catecholaminergic-acetylcholinergic imbalance hypothesis of bipolar disorder, postulating that mania is characterized by overactivity of catecholaminergic (noradrenergic, dopaminergic) systems and depression is related to the overactivity of the acetylcholinergic system [21] is right and our assumption about the common nature of bipolar disorder and essential hypertension is correct, acetylcholine also should play a role in the regulation of blood pressure**.** Although this is true but the direction of the effect is the opposite to that which we would expect from our hypothesis: cholinergic manipulations like direct cholinomimetic agents as well as cholinesterase inhibitors increase blood pressure while the muscarinic antagonist scopolamine (an effective antidepressant) decreases blood pressure [26-28].

3.3.2. White Matter Lesions

White matter lesions (WML) are more common in patients with bipolar disorder and/or hypertension compared to members of the general population. It is possible that the frequent presence of WML in bipolar disorder only reflects the frequent comorbidity of bipolar disorder with hyper-tension (which comorbidity is in line with our hypothesis) and other causes of WMH (e.g. diabetes). It is interesting that a recent paper demonstrated that the number of depressive and manic episodes is positively correlated with WML load but the correlation seems to be stronger in the case of mania. This may support our hypothesis that mania

has a more intimate relationship with cardiovascular disorders (including hypertension) than depression [29-31].

3.4. Personality and Temperamental Factors

Personality, and particularly temperamental factors have strong genetic/biological bases which in part contributes to the temporal stability of fundamental temperamental traits and their resistance to change [32]. The relationship between pyknic body habitus and cyclothymic affective temperament and manic-depressive illness was first proposed by Kretschmer [33], who was the first attempting to correlate body types and physical characteristics with personality features as well as mental disorders. For example, he emphasized the strong relationship of bipolarity ("circular madness", bipolar disorder) with obesity/metabolic disorders, atherosclerosis, hypertension and haemorrhagic stroke. This theory is supported by several subsequent studies including one of the most recent ones reporting that hypertension was over-represented in bipolar affective and anxious patients but not in unipolar depressives and schizophrenic ones [34-36].

Affective temperaments (depressive, hyperthymic, cyclothymic, irritable and anxious) are the attenuated forms and frequently the precursors of major unipolar and bipolar mood disorders. From the perspective of evolution, there are basically two temperaments: depressive and hyperthymic. Cyclothymic temperament is the successive and irritable temperament is the simultaneous manifestation of mild, subclinical "manic" and "depressive" symptoms (see vol. 85 issue 1-2 of the Journal of Affective Disorders and [32]).

Cyclothymic temperament is significantly associated with hypertension in a sample of GP patients [37]. In addition, cyclotyhmic temperament significantly predicts cardiovascular complications (myocardial infarction, angina pectoris) independently of depression, age, gender and smoking [38].

A long-term follow-up study on the temperament and long-term mortality of more than 9000 former male students (aged 16-30 years) have found that significantly increased cardiovascular mortality was related to only one out of the ten temperamental types studied: men labelled with hypomanic temperament a had significantly increased cardiovascular mortality risk (risk: 1.90 (95% CI: 1.05 to 3.44)), which mortality is strongly related to hypertension [39].

Type-A behaviour (particularly in case of urgency, impatience, anger, hostility) which is quite similar to hyperthymic/irritable temperament is significantly associated with hypertension [40]. In other words, individuals with hyperthymic temperament may have a tendency towards Type A Behavioural Pattern (TABP), and TABP persons – like hyperthymics – may have short sleep time and short snooze time [41].

3.5. Precipitating Factors

Drugs and manipulations which increase central dopamine and/or noradrenaline turnover can cause/precipitate both hypertension and mania).

a) Psychostimulants such as amphetamine, cocaine and ecstasy that increase extracellular dopamine and noradrenaline concentrations and consequently increase the blood pressure [42] also provoke manic states or induce symptoms of mania [43,44]. In addition, amphetamine administration is an acknowledged animal model of mania [23, 45, 46]. At the same time, levodopa (L-Dopa) frequently evokes mania, but rather decreases than increases blood pressure [47,48]. Atomoxetine (a selective noradrenaline reuptake inhibitor) treatment is also reported to provoke (hypo)mania in patients with ADHD and also to elevate blood pressure [49-51].

b) Yohimbine, an α_2 adrenoceptor antagonist with a mechanism of action being exactly the opposite of that of clonidine has been also considered as antidepressant (as it was mentioned already in the Bible) [52] and formerly as an aphrodisiac [53]. Yohimbine also increases blood pressure in both hypertensive [54] and in normotensive [55] subjects. However, mianserine and mirtazapine, like yohimbine, are also presynaptic α_2 adrenoceptor antagonists, but they also act on several other neurotransmitter receptors. Accordingly their effect on blood pressure is not dependent only on α_2 adrenoceptor blocking and may differ from the effect of yohimbine. Consequentially in contrast to yohimbine mirtazapine typically decreases blood pressure [56-58].

c) Dual action antidepressants (i.e. serotonin/noradrenaline reuptake inhibitors like venlafaxine and duloxetine and all TCA antidepressants, particularly the noradrenaline reuptake inhibitor desipramine) induce mania more frequently than SSRIs, and increases in the blood pressure with venlafaxine and duloxetine are also more frequent than in the case of SSRIs [7, 58-60]. This is in line with old and recent theories stating that mania is characterized by overactivity of noradrenergic and dopaminergic but not of serotoninergic systems [21]. In the case of TCAs the blood pressure-elevating effect (as the consequence of NA reuptake inhibition) is over-compensated by their hypotensive side effects, due to their alpha-1 adrenergic blockade, and this is the main difference between imipramine and venlafaxine. However, particularly due to the side effects of tricyclic anti-depressants depressed patients taking these drugs primarily at the beginning of therapy and at higher initial doses tend to show common orthostatic (postural) hypo-tension. On the contrary, long-term treatment with TCA and SNRI (but not SSRI) antidepressants increases the risk of hypertension which is in line with our hypothesis [60]. However, it is quite interesting that the noradrenaline-dopamine reuptake inhibitor bupropion does not show clinically significant blood pressure elevation and bupropion-induced (hypo)manic switch is also very rare [7,61,62].

d) Both sleep deprivation and insomnia – accompanied by increased central sympathetic/catecholaminergic activity – have been linked to increases in the incidence and prevalence of both hypertension and manic or hypomanic episodes [7,63]. Sleep deprivation which is an effective treatment for depression can induce (hypo)manic switches [7]. Moreover, sleep deprivation/circadian rhythm disruption is used to provoke mania-like symptoms in animal models of BPD [23].

e) Stressful life events (both acute and chronic) frequently contributing to sleep reduction or insomnia are very often associated with onset of both mania and essential hypertension [64-66]. In addition, early life stress and childhood adversities – which are predisposing rather than precipitating factors – are also more common in both hypertensive [67,68] and bipolar patients [69,70] than in the general population. However, it should be noted that early negative life events are not specific for bipolar disorder as they are similarly frequently reported in several other psychiatric disorders as well [70].

3.6. Illness Course

There is a sharp contrast between essential hypertension and mania (bipolar disorder) regarding their illness course. While hypertension is a chronic state (with relatively mild fluctuations), mania (bipolar disorder) is, in the majority of cases, episodic, and, in many cases it alternates with different levels of depressive symptomatology [7]. In spite of its chronic nature the onset and severity of essential hypertension exhibit a winter peak and summer reduction in countries both north and south of the equator, and it has been suggested that this reflects seasonal variations in risk factors [71]. However, the peak incidence of mania in bipolar disorder is quite the opposite [7].

3.7. Treatment Response

Some antihypertensive drugs are also effective for treating mania. As mania is characterized by the overactivity of central noradrenaline and/or dopamine turnover those antihypertensives which act primarily *via* inhibition of / blocking these neurotransmitters were also investigated in the treatment of mania. Early clinical observations showed that besides their antimanic activity many of them (Calcium channel blockers, propranolol, clonidine, and particularly reserpine) may provoke depression [72-74]. However, the depression-provoking effect of these drugs was not supported by later studies and recent meta-analyses [75-77].

a) Calcium channel blockers, like verapamil (which does not penetrate the blood–brain barrier efficiently) and nimodipine (the most lipophilic calcium channel blocker with the greatest potential to enter the brain) may be effective in the treatment of mania, but results are not unambiguous [78-82].

b) Beta adrenergic blockers as propranolol has been also found to be effective in the acute treatment of mania by some studies (on the other hand there are also some case reports on propranolol-induced mania) [83-86]. Some preclinical results indicate that carvedilol may also be effective in the treatment of mania [87].

c) Presynaptic alpha-2 agonist clonidine which decreases the release of noradrenaline is an effective antihypertensive drug and is also effective against mania [88-90].

d) Reserpine depletes chatecholamine stores and around the 1950s it has been used widely in the treatment of hypertension [91] and mania [92] and recently in cases of drug-resistant manic states [93]. Reserpine can also provoke depression as early observations showed that long-term and high-dose reserpine administration frequently causes depression or depression-like symptoms in hypertensive patients [72]. However, most recently some authors challenged the existence of reserpine-induced depression [77].

e) Alpha-methyldopa (a DOPA-decarboxylase inhibitor), a centrally acting antihypertensive drug that decreases central levels of catecholamines and serotonin has been less extensively studied [94]. Theoretically (based on its mechanism of action) alpha-methyldopa is expected to have antimanic properties. However, a small study including only 3 manic patients showed no therapeutic effect of alpha-methyldopa, although a pharmacological effect has been evidenced by a fall in blood pressure. These results are strongly limited because of the small number of patients included [95]. Like antihypertensive drugs mentioned above alpha-methyldopa also does not cause depression in patients with essential hypertension [96].

Surprisingly no studies have been published on the effect of alpha-1 adrenergic blocker antihypertensives in mania but there are several studies with them in the treatment of PTSD [97].

On the other hand those antihypertensive drugs whose mechanism of action is not related primarily to central catecholamine metabolism have never been used/tested in the treatment of mania. Therefore, it is very likely that they are not effective in treating manic states. At the same time recent research raises the possibility that the angiotensin system has several brain effects, including an inhibitory effect on the synthesis and release of norepinephrine by Angiotensine-I(1-7), and a noradrenaline release promoting effect by Angiotensine-II [98].

a) Diuretics with their simple mechanism of action decrease blood pressure without affecting central brain functions.

b) ACE-inhibitors have never been tested/used against mania, and according to early studies, ACE inhibitors do not cause depression. Furthermore, recent reviews also suggest that the depression-provoking effect of ACE inhibitors is negligible [75]. Moreover, in some cases of captopril users, a mood-elevating effect has also been reported [99-101], as well as several cases of captopril-induced mania [102,103].

c) Angiotensin receptor blockers (ARBs, another family of peripherally acting highly effective antihypertensive drugs) that are well tolerated in general, do not cause/ provoke depression as the side effect profile of these drugs are similar to placebo [104]. Very recently antimanic effect of candesartan was demonstrated in an animal model of mania [45].

Some of those first and second generation antipsychotics which effectively treat mania show a tendency for decreasing blood pressure and sometimes may induce orthostatic hypotension. One of the most serious and common side effects of several (but not all) typical antipsychotics (chlorpromazine and levomepromazine, also effective drugs against mania) is orthostatic hypotension primarily in case of drugs with postsynaptic alpha-adrenergic blockade as a side effect. However, the more pronounced (and in some cases

isolated) postsynaptic blockade of dopamine receptors by some antipsychotics (e.g. haloperidol, amisulpride etc.) does not lead to the emergence of this side effect indicating that dopamine alone is not sufficient to explain this postulated connection [105,106]. However, the relationship between antipsychotics and blood pressure is more complex, as it has been also reported that the atypical antipsychotic, clozapine during long-term treatment is associated with increased rates of hypertension [107,108].

From a historical perspective, it is interesting to note that lithium (as a bromide salt) was used firstly to treat mania in the 1800s by William Hammond. Before its re-commencement as an anti-manic agent in 1949 by John Cade into modern psychiatry, lithium – a milestone in the treatment of bipolar disorder – was tested, beside in the treatment of gout, also as an antihypertensive drug based on the supposition that cardiac failure or hypertension might benefit by a drastic reduction in the daily intake of sodium chloride. Lithium salts served as substitutes of and with a taste reminiscent to sodium chloride in this therapy. The truth is that the blood pressure-decreasing effect of lithium – both according to the literature and clinical experience – is not remarkable and is of only theoretical interest. Paradoxically, because of several cases of lithium intoxication developed during this supplementary lithium therapy of hypertensive and cardiovascular patients lithium was withdrawn from the market in the USA in the same year when the pioneering paper of Cade on lithium treatment of manic states appeared [109-112].

3.8. Comorbidity

Compared to anxiety disorders, schizophrenia and unipolar depression, hypertension is more common in bipolar disorder (particularly if we consider bipolar spectrum patients as bipolar) [35,36,113-115]. However, this comorbidity between essential hypertension and bipolar disorder is just the surface. In fact, a relevant part of (but not all) results suggests that there is an association between low blood pressure and depression, since depression at baseline can result in low blood pressure during the follow up and, vice versa, those with low blood pressure have a higher risk of developing depression [60, 116-121]. Furthermore, preexisting hypertension is a risk factor for incident bipolar disorder but not for recurrent depressive episodes [122]. In addition, preliminary results of Dale D'Mello suggest that bipolar patients with high blood pressure suffered from higher levels of mania (cited in ref [123]). Nonetheless, there are no follow-up studies in patients with bipolar disorder to monitor changes in their blood pressure during the transitions between the different phases of the disorder (i.e. in mania, euthymia and depression).

There are several psychiatric and medical disorders/ conditions frequently comorbid with both bipolar disorders and essential hypertension and these disorders/conditions that show elevated comorbidity with bipolar disorder are less commonly comorbid with unipolar depression.

a) Thyroid function is rather increased during manic and rather decreased during depressive episodes of bipolar disorder. For example, a recent study investigating patients with schizophrenia or unipolar major depression or bipolar depression or bipolar mania found that the lowest levels of TSH (suggesting an overactivation of thyroid functions) were observable among patients with bipolar mania while the highest levels of TSH (suggesting the hypofunction of the thyroid gland) were observable among patients with bipolar depression. In addition, thyroid hormone T3 has mood improving effects *via* decreasing the sensitivity of 5-HT_{1A} receptors in the brainstem with a consequential stimulation of the synthesis and release of serotonin in the cortex and hippocampus. [124-126]. Taking the above and also that hyperthyroidism is associated with elevated blood pressure it could be expected – in consonance with our hypothesis – that manic and depressive episodes are accompanied by slightly elevated and slightly decreased blood pressure values, respectively.

b) Bipolar disorder and hypertension significantly increase the risk of stroke [127,128] and according to some results this effect is stronger than the effect of unipolar MDD on the risk of stroke [129].

c) Studies show that the prevalence of panic attacks/panic disorder is significantly increased both in patients with bipolar disorder [130] and with essential hypertension [131,132]. In addition comorbid panic attacks during a depressive episode suggest a (hypo)manic switch in patients with bipolar disorder [133].

d) Prevalence of smoking is also markedly increased both in bipolar patients [134,135] and in hypertension [136]. There are results which suggest a common genetic predisposition for smoking and depression/bipolar disorder [137-139].

e) Similarly, type 2 diabetes mellitus is three times more common in bipolar patients than in the general population [140] and type 2 diabetes is also significantly more frequent in hypertensive patients [141]. There is a substantial overlap between diabetes and hypertension in etiology and disease mechanisms [142].

f) There is an increased risk of hypertension in those who consume large amounts of alcohol. Alcohol-use disorder comorbidity is equally elevated in bipolar disorder and essential hypertension. This association has been found in both cross-sectional and prospective studies in different races and this association is independent of the type of alcoholic beverage, adiposity, education, smoking and salt intake [7,143]. One could argue that alcoholism is a very common condition to be comorbid with several disorders. However, it should be noted that the elevated alcohol-use disorder comorbidity is rather characteristic of bipolar than of unipolar depression [7,144,145], and alcohol use disorder is more common among bipolar patients with predominant (hypo)manic polarity than those with predominant depressive polarity [146].

g) Evidence has consistently supported the strong association of obstructive sleep apnea syndrome (OSAS) with an increased prevalence of essential hypertension [147] and it has also been reported that the prevalence of OSAS is markedly elevated among bipolar patients [148].

h) Finally, metabolic syndrome, obesity and insulin resistance which are also significantly related to hypertension and to sleep apnea are also more common in unmedicated bipolar patients than in controls [149,150]. At the same time the type of current mood episode in bipolar disorder was not predictive of the presence of metabolic syndrome or insulin resistance [150].

As we have shown above to support our hypothesis, the comorbidity between bipolar disorder and essential hypertension is related to the (hypo)manic component of the bipolar mood disorder. On the other hand, the prevalence of essential hypertension is less frequent in unipolar than in bipolar disorder [35,36]. In addition, the frequency of smoking [134,135,151,152], panic disorder [130,153], type 2 diabetes [123,154], obstructive sleep apnoea [155] and metabolic syndrome [149] are also less common in unipolar depression than in bipolar disorder. Although metabolic syndrome is more common among patients with bipolar disorder than among patients with unipolar MDD, the more frequent use of antipsychotics and mood-stabilizers may explain this finding [156]. These facts suggest that the similar comorbidities observed in essential hypertension and bipolar disorder may indicate a shared pathophysiology between them and this association is rather specific for bipolar disorder than for unipolar major depression as has been supported not only by the lower prevalence of hypertension in unipolar than in bipolar disorder but also the equally elevated psychiatric and medical comorbidities in hypertension and bipolar disorder but not in unipolar major depression.

4. CONCLUSION

Essential hypertension and (hypo)mania share a number of similarities. While only age at onset and course (seasonality) are basically different there is an overlap between their genetics, biological background, underlying personality/temperament, precipitating factors, treatment response and comorbidity. These overlaps between essential hypertension and (hypo)mania may imply that these two clinically different disorders have a partially common central biological background.

Both essential hypertension and bipolar disorder are biphasic/bidirectional illnesses. The main difference between them in this respect is that one cannot have both elevated and decreased blood pressure concurrently, but bipolar patients frequently show manic and depressive symptoms simultaneously [157]. The existence of these manic-depressive mixed states indicates that (hypo)mania and depression are not the results of the successive over- and underactivity of the same central mood regulating system, therefore mania and depression should have different neuroanatomical substrates/locations. This fact may support our suspicion – based on the findings listed above – that not bipolar disorder as a whole but rather (hypo)mania *per se* is basically related to essential hypertension.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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