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Athanasios Koukopoulos' Psychiatry: The Primacy of Mania and the Limits of Antidepressants

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Abstract

Abstract: Background: Athanasios Koukopoulos provided a radical model for understanding depressive and manic conditions.

Objective: To review, explain, and analyze Koukopoulos' concept of the primacy of mania, with special attention to the role of antidepressants.

Method: A conceptual review of Koukopoulos' writings and lectures on this topic is given.

Results: Koukopoulos held that depressive states are caused by manic states; the former do not occur without the latter. The most common scenario of the inseparability of depressive and manic symptoms occurs in mixed states, which we estimate to represent about one-half of all depressive episodes in all patients (not just bipolar illness). In a review of the empirical evidence for this topic, we conclude that empirical evidence exists to support the primary of mania thesis in almost 80% of depressed patients. Since antidepressants worsen mania, they would be expected to worsen depression as well in this model. We provide evidence that supports this view in most persons with depressive states.

Conclusion: Koukopoulos' model of affective illness is one where manic states are the primary pathology, and depressive conditions are a secondary consequence. Hence treatment of depression with antidepressants would be less effective than treatment with mood stabilizers, since treating an effect is less successful than treating its cause. This approach would reverse current assumptions in psychiatry.

Keywords: Antidepressants, depression, efficacy, koukopoulos, mania, mixed states, rapid-cycling, temperaments

1. INTRODUCTION

The central principles of Athanasios Koukopoulos' approach to psychiatry can be summarized in two statements, one about diagnosis, and the other about treatment:

"Depression" is not just depression, but rather the effect of manic states.

'Antidepressants' are not antidepressants, but frequently are ineffective and even harmful for depressive states.

These two principles turn contemporary psychiatry upside down. They conflict with the basic assumptions of DSM/ICD diagnosis since 1980 and the basic axioms of psychopharmacology as taught by the psychiatric mainstream since the 1970s.

Koukopoulos was a radical psychiatrist, whose views were too unpopular to allow for mainstream acceptance in his lifetime. We think the future will prove that he was right.

On diagnosis, he was the main advocate for the view that most apparently depressive states are actually mixed states where manic symptoms occur along with the more predominant depressive symptoms. Not only does this occur, he argued, but the manic symptoms are the primary and most important aspects of the mood state both for diagnosis and for treatment. For diagnosis, the extensive prevalence of mixed states led Koukopoulos to conclude that most depression is manic-depression, and that so-called "unipolar" or "major depressive disorder" (MDD) is much less common and much less important than appears to be the case in mainstream DSM-based psychiatry.

On treatment, Koukopoulos was among the first clinicians to identify that antidepressants worsen the long term course of bipolar illness, causing more and more mood episodes over time, thereby producing a rapid-cycling course. Koukopoulos would practice for 50 years with minimal use of antidepressants. In his final years, he gave antidepressants to only 3% of his patients [1].

In this paper, we will explain and extend his basic views on diagnosis and treatment: We will show that depressive states are mostly part of manic-depressive illness, and thus "major depressive disorder" (MDD) as a separate entity is false. And we'll explain that antidepressants are ineffective or harmful for many depressive states, including those labeled "MDD", not just for bipolar illness, and thus have a limited role in psychopharmacology treatment.

1.1. Background

When we first encountered Athanasios Koukopoulos, it was in the setting of his yearly conferences in Rome. He was the main organizer of those conferences, which attracted many local and national Italian clinicians with an interest in depression and bipolar illness. He would give a key lecture during those conferences, and on more than one occasion, we heard him giving the signature lecture of his later years: "The Primacy of Mania" [2].

The first time we heard it, we didn't understand it.

Then we joined him and his colleagues in informal settings, and we talked about our ideas about psychiatry, the one all-consuming topic of Koukopoulos' conversation. He told us what he thought about diagnosing and treating patients, and we told him what we thought, and we listened to others.

Then the next year the same process would be repeated, and the year after. Koukopoulos would visit Boston to see family almost every year also, and again we would meet and talk about his ideas.

Over about a decade of repeated interactions, we eventually reached the point where we heard his Primacy of Mania lecture again, and at last we thought we understood it. In the last decade of our work, those ideas have transformed much of what we think about the theory and practice of clinical psychiatry as related to mood conditions. We now practice clinically quite differently in many patients than a decade ago. The change is the result of the impact of understanding Koukopoulos' theory of the primacy of mania.

1.2. The Basic Principle of the Primacy of Mania

Koukopoulos was a radical thinker. He completely turned upside down the current approach to understanding affective illness. The conventional wisdom is that depression and mania are two different states. Most people only have one state, unipolar depression, which occurs repeatedly or consistently, but without any mania. The two mood states can exist together in bipolar illness, but even then they occur in separate phases: sometimes one is depressed; sometimes manic. They rarely occur together, in "mixed episodes", which were uncommon using DSM-IV criteria, to the point that they were not even measured in DSM-IV field trials of mood disorders [3].

So the world is split into two: there is a depressed world (which is very large) and a manic world (which is small), and rarely the twain do they meet.

This is the conventional wisdom of contemporary psychiatry for the past half century, codified in DSM-III-5.

Koukopoulos rejected this approach.

There is another alternative: in this view depression and mania aren't separate and unrelated phenomena, but rather one causes the other. For about a century, this view also has been prominent, through the influence of Freud and his followers. The psychoanalytic view was that depression causes mania; mania is a reaction to depression. You are depressed, but you can't tolerate the feeling, so you take flight, unconsciously, into mania. You only *seem* happy and active and euphoric and energetic; in fact, those are all reactions to the opposite state, of feeling down and sad and blue deep down.

Koukopoulos rejected this approach too.

This psychoanalytic view held sway before, and alongside, the standard DSM view of unipolar depression. Either way, depression was prominent; mania was either uncommon or epiphenomenal, a superficial consequence of the more serious problem of depression.

The great psychoanalytic teacher, Leston Havens, used to give his own lecture about mania [4]. One of us (SNG) heard that lecture over and over again also, and didn't understand it either for some years. Havens made the point that psychoanalysts and mental health professionals in general had no difficulty empathizing with depression; but our profession has tended to denigrate mania. We see depression as profound and mania as superficial. Depression or melancholy is even claimed to produce genius; mania is associated with impulsivity and violence. We immediately intuit the fact that depression comes in grades: mild, moderate, and severe. The word "mania" automatically produces an image of only the most severe variety: the hallucinating homeless man who thinks he is Jesus Christ, and who we fear will attack us physically. You and I could admit to being depressed sometimes. We would never admit to being manic sometimes.

Havens made the point that we empathize with depression more not because it is more common or accessible to us, but rather because we discriminate against and stigmatize mania.

This is one reason why it is hard to understand Koukopoulos' concept of primacy of mania: both psychiatrists and patients have avoided mania, or viewed it superficially. Depression, in contrast, seems more profound. Koukopoulos wanted to reverse terms: we need to take mania seriously, and then we'll see that depression is a consequence, not a cause.

1.3. The Evidence

There are a number of different lines of evidence for the primary of mania. The question is: Does depression ever happen without some form of mania? The answer, from Koukopoulos, is no. Let us see how he explains this idea.

1.3.1. Bipolar Depression

First, there is straightforward bipolar illness. In this DSM-based diagnosis, most patients have manic or hypomanic episodes, as defined with DSM criteria, followed by depressive episodes. Mania precedes depression temporally, and Koukopoulos argues, causally. Patients get depressed after mania because mania causes depression. What goes up must come down.

How frequent is this phenomenon? We can estimate it this way: About one-fifth of all depressive episodes, using DSM criteria, occur in persons who also meet DSM criteria for bipolar illness, type I or type II [5]. So 20% of depressive episodes are bipolar. Most of these episodes (about 75%) involve a pattern of mania/hypomania followed by depression (M-D), rather than depression preceding mania (D-M) [5]. So we can estimate that 15% of all depressive episodes can be said to be caused by mania if we accept the notion that temporal precedence relates to causality.

1.3.2. Mixed Depression

Another large category of persons with depressive episodes have manic episodes during the depressive episodes, *i.e.*, mixed states. This group of patients was of most interest to Koukopoulos. These mixed states can be defined in different ways, outside of DSM constraints. The simplest approach is the bipolarity specifier described by Benazzi [6]; on this definition a

mixed state would be defined by a clinical depressive episode in which three or more DSM-defined manic symptoms occurred for any amount of time (not limited to the 4 days or longer DSM criterion of duration for hypomania or one week or longer for mania). On this definition, Angst and colleagues found that 47% of a large sample of 5635 outpatients with depressive episodes met the mixed state definition [7]. One could also use Koukopoulos' own definition of "mixed depression", which is even broader than the bipolarity specifier because it goes beyond DSM criteria [8]. In Koukopoulos' definition, as described in more detail below, mixed depression involves the presence of a clinical depressive episode along with psychomotor excitation, which can be limited to psychomotor agitation and/or marked rage. Using Koukopoulos' definition of mixed depression, in his own Rome clinic, 51% of 435 consecutive patients with clinical depressive episodes had mixed depressive states [9].

If we combine the approach of Angst and Benazzi on one hand, and Koukopoulos on the other, we can conservatively estimate that about 50% of all depressive episodes are mixed with manic symptoms, and thus are mixed states, not pure depression. The theory of the primacy of mania would apply if we accept the notion that these mixed states are driven by their manic components; in other words, one cannot separate the depressive from the manic symptoms; they come from the same pathophysiological source. Without the manic symptoms, the depressive symptoms would not occur.

So here are another 50% of depressive episodes, the largest chunk, which would not happen without mania. Combined with the 15% of classic manic-depressive cycles in bipolar illness, we account for the majority, 65%, of depressive episodes so far, meeting the definition of the primacy of mania.

1.3.3. Affective Temperaments

What about the remaining 35%? Are they purely depressive cases, so-called "unipolar" depression? Now we turn to the concept of affective temperaments, as expounded most definitively in recent years by Akiskal [10], a good friend of Koukopoulos. Previously, these temperaments were described by Kraepelin, and later Kretschmer in more detail. The idea was that mild mood symptoms could occur in persons with mood illnesses, in between the severe episodes, and these mild symptoms were present all the time, as part of one's temperament. These conditions were defined as dysthymia, hyperthymia, cyclothymia (mild depressive, manic, and manic-depressive symptoms, respectively). Hyperthymia was left out of DSM-III out of apparent ignorance, and has remained unknown to most clinicians since 1980. These concepts were rarely used in American psychiatry in any case after their careful elaboration by Kretschmer around the 1920s [11].

The frequency of hyperthymia or cyclothymia in patients with unipolar depression has not been well studied. One small report found that about 72% of a unipolar sample (n=36) was diagnosable with cyclothymia using the TEMPS scale, and 31% were diagnosable with hyperthymia [12]. (Some patients met both definitions). If these pilot data are confirmed, one could estimate that about one-half of patients with unipolar depression may have affective temperaments of hyperthymia or cyclothymia.

This possibility is supported by an analysis of 219 patients from Koukopoulos' own practice in Rome [1], where 33% were diagnosed with MDD, 20% diagnosed with bipolar illness, and the rest with other psychiatric conditions. Overall, using clinical diagnostic assessment, hyperthymic temperament was present in 63% of the total sample, and cyclothymic temperament in 13%, meaning that 76% of the overall sample had some kind of manic temperament. The MDD subsample was not analyzed separately for temperament prevalence, but assuming a higher prevalence of manic temperaments in the bipolar subsample, it could be inferred that a substantial proportion of the MDD subsample would also have manic affective temperaments.

If these inferences prove correct, it would seem reasonable to conclude that perhaps one-third or more of patients with non-bipolar depression will have manic temperaments, either hyperthymic or cyclothymic. If so, these calculations would explain one-third or so of the 35% of remaining persons with depressive episodes (*i.e.*, about 12%). Koukopoulos' view would be that long-standing hyperthymic or cyclothymic temperaments predispose such persons to depressive episodes. Again, manic symptoms cause depressive symptoms.

We now have explained 77% of all persons traditionally diagnosed with severe clinical depressive episodes (50% + 15% + 12%). This would be almost 4 out of 5 of such persons.

1.3.4. Neurotic Depression

What of the remainder? In our view, the concept of neurotic depression, long ago rejected by DSM-III in 1980, explains those who have notable depressive conditions but do not have any variety of manic-depressive illness.

Neurotic depression refers to mild to moderate chronic anxiety, occurring along with mild to moderate chronic depressive symptoms [13]. It is constant and chronic, not episodic, and anxiety symptoms are problematic but not usually episodically severe, as in mixed manic-depressive states. There is no rage or marked anger and libido is not high, nor are there racing thoughts or impulsive behavior. Suicide is uncommon, though passive suicidal ideation can occur. Symptoms are usually mild, but highly sensitive to psychosocial environment; thus brief exacerbations can occur, in the setting of work or personal stress, such that patients may meet more severe clinical criteria for a depressive episode, but these exacerbations resolve quickly, usually within weeks, rarely up to months. They are not spontaneous and severe, lasting routinely for months, as is the case in many patients with manic-depressive illness.

Koukopoulos had not proposed this idea, and was hesitant about it. The apparent overlap would be in the concept of anxiety: Mixed states involved marked anxiety; neurotic depression involves notable anxiety. But that is where the similarity ends. Applying the classic diagnostic validators of genetics, course, and biology, neurotic depression and mixed depression are as different as apple pie and steak. Mixed depression is part of manic-depressive illness (MDI); it occurs in families of persons with MDI; it is highly genetic (about 80-90% heritability, like Alzheimer's dementia) [14]. It has a course of severe episodes that begin around age 20 and come and go in a regular pattern, with more or less normal or less symptomatic intervals between episodes. Its neurobiology involves, among other things, abnormal circadian rhythm biology, enlarged amygdalar volume, and hippocampal atrophy [5]. Neurotic depression is much less genetic (about 50% genetic heretability, like personality traits such as shyness) [13]. It begins early in childhood, since it represents being high on the personality trait of neuroticism;

such temperament traits are identifiable as early as toddlerhood. It is not episodic, but since it represents basic temperament, it is constant. It involves no known neurobiological changes in the brain of long-standing nature, and circadian rhythm biology has not been shown to be abnormal [13].

The concept of neurotic depression is old, but it was advanced most clearly in the 20th century by Sir Martin
Roth in the UK [15]. Unfortunately, his rationale for the nosological validity of this concept, as outlined above, was rejected by the DSM-III leadership and others in the psychiatric hierarchy of his era.

2. Antidepressant inefficacy and harms

Once the nosology of depression is understood through the prism of the primacy of mania, we can better understand the central treatment principle of Koukopoulos' approach to psychiatry: antidepressants are ineffective, and sometimes harmful.

A consistent theme to Koukopoulos' thinking about all these depressive states is that so-called "antidepressants" are not antidepressants, *i.e.*, they are not effective for most depressive states. Let us review this evidence briefly, beginning with bipolar depression, followed by mixed depression, focusing on his own work, followed by a look at data in neurotic depression.

2.1. Bipolar Depression

We and others have previously published randomized clinical trials and meta-analyses showing that antidepressants basically are ineffective in acute and maintenance treatment of bipolar depression [16,17].

Koukopoulos' own clinical experience was documented in his papers and in our analysis of his later practice, as described in the mixed depression section below. In his own work, he was among the first to report that patients with rapid-cycling bipolar illness tended to receive antidepressants. When antidepressants were stopped, such patients had an improved course, suggesting that the association was causal. An early randomized trial with tricyclic antidepressants had suggested a causal link [18], and three decades later, a second replication with modern antidepressants by our group confirmed Koukopoulos' observation [19]. Nonetheless, the psychiatric profession has been very resistant to the notion that antidepressants can cause rapid-cycling, thereby worsening the long-term course of bipolar illness. Prominent researchers have published opposite conclusions, denying such a causal association between antidepressant and rapid-cycling, based on observational data [20], and others have repeatedly cited those data to deny the link. This has occurred despite the obvious first law of clinical epidemiology and evidence-based medicine [21]: observational data do not disprove randomized data. Rather the reverse is the case.

2.1.1. The Resistance of the Profession and the 2013 ISBD Task Force

As noted previously, Koukopoulos was among the first clinicians to identify that antidepressants worsen bipolar illness, causing a rapid-cycling course. He practiced with minimal use of antidepressants, giving them to only 3% of his patients [1].

He made his observations beginning in the 1960s as he began his practice in Rome and as antidepressants were introduced into clinical practice. He published his insight as early as 1980 [22]. He would practice for about half a century, but he spent three decades trying to convince a recalcitrant profession that his unwelcome observation was correct. For the last 40 years, his insight has been resisted vehemently by clinicians and even by bipolar researchers. Psychiatry has been, and remains, a pro-antidepressant profession. For the majority of his working life, Koukopoulos faced immense resistance and skepticism.

In the final year of his life, as a member of the 2013 International Society for Bipolar Disorders' Task Force on antidepressants [23], Koukopoulos was faced with continued resistance. Despite the evidence reviewed above, with multiple negative RCTs showing that antidepressants were equivalent to placebo, the majority of over 60 bipolar experts on that task force were unwilling to simply state the scientific truth: that antidepressants are equivalent to placebo, *i.e.*, ineffective in acute bipolar depression, at least in type I subtype. (Koukopoulos and we believe that they are also ineffective in type II bipolar illness, despite some RCT findings that are mixed, but that is another matter discussed elsewhere [24]).

The task force was unwilling to make a clear statement against antidepressant use in bipolar depression, but after decades of studies, it was clear that it could no longer continue the practice of prior task forces, which had claimed that antidepressants were effective in bipolar depression [25]. The task force could not make a recommendation that antidepressants should be used in bipolar depression, unlike prior task forces, but it refused to state that they should *not* be used. Instead, it made every effort to let clinicians use their judgment in making such decisions; in effect, it refused to commit.

One of us (SNG) was not happy with this refusal
to follow the scientific evidence when it showed
inefficacy, in contrast to no hesitation in recommendation of psychotropic medications whenever similar studies showed evidence of efficacy. Koukopoulos was more measured in his reaction.

After a lifetime of struggle, he realized that he had made incremental progress: At least now bipolar experts were willing to accept that they could not heartily and without reservation recommend antidepressant use in bipolar depression. That was better than the past, when they had made such recommendations.

Koukopoulos accepted that outcome as progress, which it was.

One might wish, nonetheless, that it would take less than a lifetime to draw such minimal conclusions for a reasonably replicated scientific literature.

2.2. Mixed Depression

Koukopoulos' papers on antidepressant effects in mixed depression again reflect his clinical practice. Recently, Sani and colleagues published data from Centro Lucio Bini in Rome, which Koukopoulos had organized and led [1]. In 219 patients in his practice who met his criteria for mixed depression, about one-half of cases of mixed depression (50.7%) were caused by antidepressants. Suicide attempts were 2.5 times more frequent if mixed depressive states were associated with antidepressants than if such mixed states occurred without antidepressants.

Serotonin reuptake inhibitors caused mixed depression about as frequently as tricylic antidepressants (38.5% versus 45% respectively). Type II bipolar patients, as opposed to type I, were more likely to receive antidepressants which caused mixed depression. Concomitant treatment with neuroleptics reduced the frequency of mixed depression as a result of antidepressant use.

Before treatment by Koukopoulos and his colleagues, 57% of the sample had been treated with antidepressants, and only 5% received mood stabilizers (lithium, valproate, or carbamazepine), and 9% received neuroleptics. After treatment with the Rome group, the treatment was reversed almost completely, with only 2.7% receiving antidepressants, and about one-third each receiving mood stabilizers or neuroleptics (31.5% and 30% respectively). A large subgroup, 25%, received electroconvulsive therapy (ECT) for acute mood improvement.

With this approach, in a mean of 1.3 years of follow-up, these patients showed a marked improvement in depression symptoms with Hamilton Depression Rating Scale (HDRS) scores improving from a mean of 27.9 to 8.0. Further, almost one-half of the sample (45%) did not relapse in over a year of follow-up at all, while 27% had a mild relapse if it occurred (hypomania or mild depression). Only 17% had a full depressive episode in follow-up, and only 1% made suicide attempts.

In another analysis combining data from Koukopoulos' Rome group along with the International Mood Network (IMN), we collaborated with other colleagues to conduct a diagnostic validity study of Koukopoulos' criteria for mixed depression in a sample of 435 mood illness patients (139 with bipolar illness, 296 with "MDD"). Using classic standard diagnostic validators of course, genetics, and treatment effects, we confirmed that his criteria identified a separate group of patients which could be identified with very good specificity (86%) and good sensitivity (76%), as opposed to other more purely depressed patients. We also identified very high positive predictive value (86%) in that sample, thus producing quite low false positive rates. Negative predictive value was also good (75%). The most common symptoms were absence of psychomotor retardation (84%), mood lability or marked mood reactivity (78%), and psychic agitation or inner tension (75%).

In his final years Koukopoulos tried to inform the DSM 5 task force group about his depressive mixed state concept. Unfortunately, he was not heard. In his final publications in the last few months of his life, he published two final reviews of the claim of the DSM-5 task force that "overlapping" mood symptoms (irritability, psychomotor activation, inner tension), which occur in both mania and depression, should be excluded from the mixed episode modifier. In a comprehensive review [26], Koukopoulos and Sani analyzed the literature cited by the DSM-5 task force, which consisted of 7 studies, in support of the DSM-5 definition. They showed that 3 of those 7 studies did not provide any data in support of the DSM-5 definition. The other 4 studies showed that the DSM-5 definition would identify only 7-12% of persons with depressive episodes as having mixed features, a small number that is in the same range as the narrow definition used in DSM-IV. In other words, DSM-5 was not really broadening the definition of

mixed states; it was only defining it differently to produce the same result. Koukopoulos and Sani identified a number of other studies, which the DSM-5 task forced had ignored, which provided empirical evidence for the diagnostic validity of a broader definition of mixed states, as reviewed previously in this paper.

In another critique [27], Koukopoulos and colleagues critiqued the DSM-5 definition conceptually. They noted that by requiring euphoric rather than irritable mood, the DSM-5 definition would reflect mixed hypomania, rather than mixed depression. They also held that exclusion of the most common features of mixed states, namely irritability and agitation, because they are claimed to be nonspecific, was illogical. It was like refusing to allow "headache" as a criterion for the diagnosis of migraine as opposed to other types of pain in the head.

This would be his last paper that he saw published.

2.3. Neurotic Depression

Antidepressants are not effective for neurotic depression, not because they don't "work" but because everything "works", and nothing really works. To explain: neurotic depression involves mild to moderate depressive symptoms [15]. Even in the brief exacerbations that meet clinical depressive episode criteria, these patients usually have what are considered mild or moderate clinical depressive episodes (*e.g.*, Hamilton Depression Rating Scale scores in the 18-28 range). Meta-analyses of hundreds of randomized clinical trials (RCTs) of antidepressants in so-called major depressive disorder (MDD) have been conducted to examine effects of antidepressants on mild versus moderate versus severe clinical depressive episodes. In our reanalysis of those data [28], we confirmed the report by others that antidepressants were not more effective than placebo for mild clinical depressive episodes, although they were more effective for moderate to severe clinical depressive episodes. The important clinical nuance is that placebo was very effective in mild clinical depressive episodes, but less so with increasing severity of depression. Thus, the drug-placebo difference involved increasing placebo efficacy for mild depressive states, not decreasing drug efficacy for those states.

In other words, most patients with mild depression improved, whether they received antidepressants or placebo. It wasn't that neither worked; both "worked." Whatever this "working" means – we think it involves the natural history of rapid resolution of brief exacerbations in neurotic depression – the "benefit" seen with antidepressants was not because of the pharmacological effects of those agents.

In reality, though, nothing is working because the temperament trait of high neuroticism does not change. These patients may improve from their brief depressive exacerbations, but they go back to their baselines of mild to moderate unrelenting depression and anxiety, just below the threshold for official definitions of full clinical depressive episodes. These patients remain subsyndromally symptomatic and unhappy and notably dysfunctional. Long-term antidepressant use and even some psychotherapies, like cognitive-behavioral therapy, may improve this neuroticism, a long-term chronic mild to moderate depressive/anxious baseline, but they do not remove it altogether [29].

CONCLUSION

It is difficult to provide a brief conclusion to a summation of such radical ideas as we tried to explain in this paper. If an attempt were to be made, one approach would be to say that the basic DSM/ICD approach to depression nosology is false, and the basic mainstream psychopharmacology approach to treatment of "depression" with "antidepressants" is false. The reasons for these falsehoods are complex, and were explained in this paper; the signposts to those explanations are Koukopoulos' concept of the primacy of mania and the consequent reexamination of the psychopharmacology treatment literature on the basis of this new mood nosology showing that antidepressants have much fewer benefits and many more harms than has been believed.

These are the central radical ideas of Koukopoulos' conception of psychiatry, and they were not accepted by his contemporaries in his half century of lifelong practice. We predict the future profession will find that Koukopoulos' work was correct and ahead of his time. Koukopoulos once said that there was more truth in one sentence of Nietzsche than in the claims of evidence-based medicine. Like this philosopher whom he esteemed, one can say of Koukopoulos that he was born posthumously, and that when he wrote and spoke his ideas, those who could understand them had not yet been born.

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CONFLICT OF INTEREST

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REFERENCES

1. Sani G., Napoletano F., Vöhringer P.A., Sullivan M., Simonetti A., Koukopoulos A., Danese E., Girardi P., Ghaemi N. Mixed depression: clinical features and predictors of its onset associated with antidepressant use. *Psychother. Psychosom.* 2014;**83**(4):213–221. [http://dx.doi.org/10.1159/000358808]. [PMID: 24970376]. [PubMed] [Google Scholar]

2. Koukopoulos A., Ghaemi S.N. The primacy of mania: a reconsideration of mood disorders. *Eur. Psychiatry.* 2009;**24**(2):125–134. [http://dx.doi.org/10.1016/j.eurpsy.2008.07.006]. [PMID: 18789854]. [PubMed] [Google Scholar]

3. Keller M.B., Hanks D.L., Klein D.N. Summary of the DSM-IV mood disorders field trial and issue overview. *Psychiatr. Clin. North Am.* 1996;**19**(1):1–28. [http://dx.doi.org/10.1016/S0193-953X(05)70270-7]. [PMID: 8677213]. [PubMed] [Google Scholar]

4. Havens L.L., Ghaemi S.N. Existential despair and bipolar disorder: the therapeutic alliance as a mood stabilizer. *Am. J. Psychother.* 2005;**59**(2):137–147. [PMID: 16170918]. [PubMed] [Google Scholar]

5. Goodwin F.K., Jamison K.R. *Manic Depressive Illness.* 2nd ed. New York: Oxford University Press; 2007. [Google Scholar]

6. Benazzi F. Defining mixed depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* 2008;**32**(4):932–939. [http://dx.doi.org/10.1016/j.pnpbp.2007.12.019]. [PMID: 18234411]. [PubMed] [Google Scholar]

7. Angst J., Azorin J.M., Bowden C.L., Perugi G., Vieta E., Gamma A., Young A.H., BRIDGE Study Group Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: the BRIDGE study. *Arch. Gen. Psychiatry.* 2011;**68**(8):791–798. [http://dx.doi.org/10.1001/archgenpsychiatry.2011.87]. [PMID: 21810644]. [PubMed] [Google Scholar]

8. Koukopoulos A., Sani G., Koukopoulos A.E., Manfredi G., Pacchiarotti I., Girardi P. Melancholia agitata and mixed depression. *Acta Psychiatr. Scand. Suppl.* 2007;(433):50–57. [http://dx.doi.org/10.1111/j.1600-0447.2007.00963.x]. [PMID: 17280571]. [PubMed] [Google Scholar]

9. Sani G., Vöhringer P.A., Napoletano F., Holtzman N.S., Dalley S., Girardi P., Ghaemi S.N., Koukopoulos A. Koukopoulos' diagnostic criteria for mixed depression: a validation study. *J. Affect. Disord.* 2014;**164**:14–18. [http://dx,doi,org/10,1016/j,jad, 2014.03.054]. [PMID: 24856547]. [PubMed] [Google Scholar]

10. Rihmer Z., Akiskal K.K., Rihmer A., Akiskal H.S. Current research on affective temperaments. *Curr. Opin. Psychiatry.* 2010;**23**(1):12–18. [http://dx.doi.org/10.1097/YCO.0b013e32833299d4]. [PMID: 19809321]. [PubMed] [Google Scholar]

11. Kretschmer E. *Physique and Character.* London: Kegan and Paul; 1925. [Google Scholar]

12. Goto S., Terao T., Hoaki N., Wang Y. Cyclothymic and hyperthymic temperaments may predict bipolarity in major depressive disorder: a supportive evidence for bipolar II1/2 and IV. *J. Affect. Disord.* 2011;**129**(1-3):34–38. [http://dx.doi.org/10.1016/j.jad.2010.07.016]. [PMID: 20699193]. [PubMed] [Google Scholar]

13. Ghaemi S.N. Why antidepressants are not antidepressants: STEP-BD, STAR*D, and the return of neurotic depression. *Bipolar Disord.* 2008;**10**(8):957–968. [http://dx.doi.org/10.1111/j.1399-5618.2008.00639.x]. [PMID: 19594510]. [PubMed] [Google Scholar]

14. Bienvenu O.J., Davydow D.S., Kendler K.S. Psychiatric diseases versus behavioral disorders and degree of genetic influence. *Psychol. Med.* 2011;**41**(1):33–40. [http://dx.doi.org/10.1017/ S003329171000084X]. [PMID: 20459884]. [PMC free article] [PubMed] [Google Scholar]

15. Roth S.M., Kerr T.A. The concept of neurotic depression: A plea for reinstatement. In: Pichot P., Rein W., editors. *The clinical appraoch in psychiatry.* Paris, France: Synthelabo; 1994. pp. 339–368. [Google Scholar]

16. Sidor M.M., Macqueen G.M. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. *J. Clin. Psychiatry.* 2011;**72**(2):156–167. [http://dx.doi.org/10.4088/JCP.09r05385gre]. [PMID: 21034686]. [PubMed] [Google Scholar]

17. Ghaemi S.N., Wingo A.P., Filkowski M.A., Baldessarini R.J. Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks. *Acta Psychiatr. Scand.* 2008;**118**(5):347–356. [http://dx.doi.org/10.1111/j.1600-0447.2008.01257.x]. [PMID: 18727689]. [PMC free article] [PubMed] [Google Scholar]

18. Wehr T.A., Goodwin F.K. Rapid cycling in manic-depressives induced by tricyclic antidepressants. *Arch. Gen. Psychiatry.* 1979;**36**(5):555–559. [http://dx.doi.org/10.1001/archpsyc.1979. 01780050065007]. [PMID: 435015]. [PubMed] [Google Scholar]

19. Ghaemi S.N., Ostacher M.M., El-Mallakh R.S., Borrelli D., Baldassano C.F., Kelley M.E., Filkowski M.M., Hennen J., Sachs G.S., Goodwin F.K., Baldessarini R.J. Antidepressant discontinuation in bipolar depression: a Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized clinical trial of long-term effectiveness and safety. *J. Clin. Psychiatry.* 2010;**71**(4):372–380. [http://dx.doi.org/10.4088/ JCP.08m04909gre]. [PMID: 20409444]. [PubMed] [Google Scholar]

20. Coryell W., Solomon D., Turvey C., Keller M., Leon A.C., Endicott J., Schettler P., Judd L., Mueller T. The long-term course of rapid-cycling bipolar disorder. *Arch. Gen. Psychiatry.* 2003;**60**(9):914–920. [http://dx.doi.org/10.1001/archpsyc.60.9. 914]. [PMID: 12963673]. [PubMed] [Google Scholar]

21. Sackett D.L., Strauss S., Richardson W.S., Rosenberg W., Haynes R.B. *Evidence Based Medicine.* 2nd ed. London: Churchill Livingstone; 2000. [Google Scholar]

22. Kukopulos A., Reginaldi D., Laddomada P., Floris G., Serra G., Tondo L. Course of the manic-depressive cycle and changes caused by treatment. *Pharmakopsychiatr. Neuropsychopharmakol.* 1980;**13**(4):156–167. [PMID: 6108577]. [PubMed] [Google Scholar]

23. Pacchiarotti I., Bond D.J., Baldessarini R.J., Nolen W.A., Grunze H., Licht R.W., Post R.M., Berk M., Goodwin G.M., Sachs G.S., Tondo L., Findling R.L., Youngstrom E.A., Tohen M., Undurraga J., González-Pinto A., Goldberg J.F., Yildiz A., Altshuler L.L., Calabrese J.R., Mitchell P.B., Thase M.E., Koukopoulos A., Colom F., Frye M.A., Malhi G.S., Fountoulakis K.N., Vázquez G., Perlis R.H., Ketter T.A., Cassidy F., Akiskal H., Azorin J.M., Valentí M., Mazzei D.H., Lafer B., Kato T., Mazzarini L., Martínez-Aran A., Parker G., Souery D., Ozerdem A., McElroy S.L., Girardi P., Bauer M., Yatham L.N., Zarate C.A., Nierenberg A.A., Birmaher B., Kanba S., El-Mallakh R.S., Serretti A., Rihmer Z., Young A.H., Kotzalidis G.D., MacQueen G.M., Bowden C.L., Ghaemi S.N., Lopez-Jaramillo C., Rybakowski J., Ha K., Perugi G., Kasper S., Amsterdam J.D., Hirschfeld R.M., Kapczinski F., Vieta E. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am. J. Psychiatry.* 2013;**170**(11):1249–1262. [http://dx.doi.org/10.1176/appi.ajp. 2013.13020185]. [PMID: 24030475]. [PMC free article] [PubMed] [Google Scholar]

24. Ghaemi S.N., Hsu D.J., Soldani F., Goodwin F.K. Antidepressants in bipolar disorder: the case for caution. *Bipolar Disord.* 2003;**5**(6):421–433. [http://dx.doi.org/10.1046/j.1399-5618.2003.00074.x]. [PMID: 14636365]. [PubMed] [Google Scholar]

25. Hirschfeld R.M., Bowden C.L., Gitlin M.J., Keck P.E., Perlis R.H., Suppes T., Thase M.E. American Psychiatric Association practice guideline for the treatment of patients with bipolar disorder (revision). *Am. J. Psychiatry Suppl.* 2002;**159**:1–50. [PubMed] [Google Scholar]

26. Koukopoulos A., Sani G. DSM-5 criteria for depression with mixed features: a farewell to mixed depression. *Acta Psychiatr. Scand.* 2014;**129**(1):4–16. [http://dx.doi.org/10.1111/acps.12140]. [PMID: 23600771]. [PubMed] [Google Scholar]

27. Koukopoulos A., Sani G., Ghaemi S.N. Mixed features of depression: why DSM-5 is wrong (and so was DSM-IV). *Br. J. Psychiatry.* 2013;**203**(1):3–5. [http://dx.doi.org/10.1192/bjp.bp. 112.124404]. [PMID: 23818531]. [PubMed] [Google Scholar]

28. Vöhringer P.A., Ghaemi S.N. Solving the antidepressant efficacy question: effect sizes in major depressive disorder. *Clin. Ther.* 2011;**33**(12):B49–B61. [PMC free article] [PubMed] [Google Scholar]

29. Tang T.Z., DeRubeis R.J., Hollon S.D., Amsterdam J., Shelton R., Schalet B. Personality change during depression treatment: a placebo-controlled trial. *Arch. Gen. Psychiatry.* 2009;**66**(12):1322–1330. [http://dx.doi.org/10.1001/archgenpsychiatry.2009.166]. [PMID: 19996037]. [PMC free article] [PubMed] [Google Scholar]