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Aripiprazole and Cariprazine for Bipolar Disorder?

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Abstract

In this article, the present author, a research psychologist and measurement expert, evaluates the major clinical trials used to support the use of aripiprazole and the chemically almost identical cariprazine for treating bipolar disorder. The main problem with the trials is that they were conducted mainly with outpatients, who on average were only moderately manic in the mania studies and only moderately depressed in the depression studies. The effectiveness of aripiprazole and cariprazine in treating *moderate* mania, most likely hypomania, and *moderate* depression, was far from encouraging. Aripiprazole produced just 7% greater reduction of mania symptoms than did placebo treatment, and just 1% greater reduction of depression symptoms than did placebo treatment when administered, as is common practice, with an SSRI or SNRI antidepressant. Cariprazine proved to be not much better because at the high dosage level of 3.0 mg/day to 12.0 mg/day, cariprazine produced only 9% greater reduction of mania symptoms than did placebo treatment, and at the typical low dosage of 1.5 to 3.0 mg/day produced just 4% greater reduction of depression symptoms than did placebo treatment. Moreover, as the pharmaceutical industry has long suspected, there is a massive placebo effect associated with these two drugs, especially for depression. These findings imply that government regulatory authorities' approval of aripiprazole and cariprazine as mood stabilizers for treating bipolar disorder is dubious. Nevertheless, the possibility remains that the purported mood-stabilizing mechanism of these two medicines is activated only with patients presently experiencing *severe* mania or *severe* depression, a possibility that requires an in-hospital clinical trial or, at the very least, a longitudinal analysis of bipolar patients' treatment records. Furthermore, an appendix to the present article demonstrates that the measures used in the trials, the Young Mania Rating Scale and the Montgomery-Asberg Depression Rating Scale, are deficient and that a briefer combination measure focusing only on the core symptoms of bipolar disorder should be used.

Keywords

Bipolar Disorder, Mania, Depression, Mood Stabilizers, Clinical Trials, Problems with Current Measures

1. Introduction

It costs a pharmaceutical company approximately $1 billion to invent, develop and test a new psychoactive drug [1]. Following this process, which, depending on the success of early efficacy and safety results, can take up to 20 years, the company then has to submit the drug's final so-called stage 3 clinical trial results to the U.S. Food and Drug Administration for approval to put the drug on the market. This is an arduous and fraught process, with U.S. National Institute of Mental Health representative Thomas R. Insel pointing to the increasing failure of new psychoactive drugs to perform better than a placebo in clinical trials as a major obstacle to approval [2]. However, there is likely to have been a lot of pressure on the FDA to approve new drugs given that the pharmaceutical companies, via industry user fees, contribute the major part, reported to be 65% [3], of the FDA's annual human drug-testing budget. It is in this somewhat skeptical light that the present author, in this article, evaluates the clinical trial evidence relied on by the FDA to approve aripiprazole and cariprazine for treating bipolar disorder.

Bipolar disorder is a mental disorder characterized by severe and typically sudden mood swings, either up into *mania* (a lifetime manic episode being the only symptom necessary for a diagnosis of the serious form of bipolar disorder) or, for an estimated 70% to 80% of bipolar disorder sufferers, down into *depression* (which happens either immediately after the manic episode or more often independently and lasts much longer than a manic episode) [4]. Bipolar disorder occurs in a severe and always dysfunctional form known as Bipolar I which requires at least one lifetime fully manic episode and has an estimated annual prevalence in the U.S. of about 1% (1 in 100 persons), and in a less severe and less dysfunctional form known as Bipolar II which requires only a lifetime mild or so-called hypomanic episode plus at least one lifetime major depressive episode and has a similar 1% (1 in 100 persons) estimated annual prevalence [5] [6]. These prevalence percentages hardly differ at all worldwide [7].

One major problem for research into bipolar disorder is that it is notoriously difficult to *diagnose*—both by psychiatrists [8] and, before that, by primary-care physicians [9]. It is difficult to diagnose for several reasons. Firstly, Hirschfeld and colleagues reported from a large-scale U.S. survey of patients with bipolar disorder that a very high 70% of them were initially misdiagnosed, and that a diagnosis of bipolar disorder required an average of 10 years and visits to four physicians before it was correctly reached [10]. Secondly, many of those who experience a manic episode do not remember it, and those who *do* have some mem-

ory of being in this highly enjoyable state are unlikely to think they need to see a doctor about it [11]. Secondly, if they do see a doctor, it is more likely to be for the consequent depression, which in turn means the doctor is likely to misdiagnose bipolar disorder as major depressive disorder [11] [12]. Lastly, because bipolar sufferers in the depressive phase are likely to be hyper-anxious and agitated as well as depressed, they are often misdiagnosed as having a primary complaint of generalized anxiety disorder [9].

Bipolar I disorder, once diagnosed, is very difficult to *treat*. If the patient is misdiagnosed as having major depression, too heavy a dosage of a serotonin-boosting antidepressant can induce a manic episode or induce more rapid cycling of depressive episodes, and if misdiagnosed as generalized anxiety disorder, the patient is likely to be treated with antianxiety medication that does little to alleviate either depression or mania [8] [11]. A further very substantial problem is that only about two in three bipolar disorder sufferers seem to *respond* to medication—and even if they do experience periods of temporary recovery and normal functioning, the threat of relapse is always around the corner [4]. Moreover, those who *do* respond to medication do not seem to respond to the same *type* of medication, and even after responding to one medication may have to be switched to another if, as often happens, the present medication appears to have lost its effectiveness [12]. This perplexing state of affairs has led to the frank admission by leading Australian bipolar disorder specialist Gordon Parker [13] that treatment of bipolar disorder is basically "trial and error".

Psychoactive medications have to be shown to work with both forms of bipolar disorder, including most importantly Bipolar I, the severe, hospitalized form. The typical medication for Bipolar 1 disorder patients consists of an antipsychotic to control manic episodes and an antidepressant to control depressive episodes. However, despite several decades of this dual medication treatment, the fact remains that the lifetime prevalence of Bipolar I disorder has not changed since the first single-medicine mood stabilizer—the naturally occurring salt compound *lithium* (lithium carbonate)—was found to be effective with bipolar patients by Australian psychiatrist John Cade back in the 1940s [4]. Neither the older so-called *typical* antipsychotics such as haloperidol and chlorpromazine (which are dopamine blockers) nor the newer so-called *atypical* antipsychotics such as quetiapine and risperidone (which are supposed to be dopamine blockers and serotonin boosters, thus mood stabilizers) have proved any more effective than lithium [2].

1.1. Two New Mood Stabilizers

The hope of a more effective atypical antipsychotic was raised by the invention of the two drugs reviewed in this article. The first of these, invented some 20 years ago, was *aripiprazole* (brand name Abilify but now available as a generic) and the second and more recent was the chemically similar *cariprazine* (brand names Vraylar in the U.S., Reagila in the U.K. and elsewhere). However, we

really do not know how any psychoactive medication, let alone mood stabilizer medication, actually works [4]. Indeed, psychiatrist Dr. Stephen Stahl [14], who consults to Allergan, the manufacturer of Vraylar in the U.S., is on record as admitting that "the mechanism of action of Vraylar is unknown" (p. 4). By inference, since the two drugs are chemically almost identical, his comment would also apply to Abilify.

The best *guess* as to how a mood stabilizer such as aripiprazole or cariprazine would work to control bipolar disorder is what is known as the *dopamine hypothesis* [4] [15]. The dopamine hypothesis is as follows: mania is thought to be caused by too *much* dopamine in the brain, whereas depression is thought to be caused by too *little* dopamine in the brain. Aripiprazole [16] [17] [18] and cariprazine [19] [20] [21] [22] are usually described in the literature not just as one of the newer atypical antipsychotics but as "partial dopamine boosters." But the term partial dopamine booster is an inadequate description because they supposedly work on dopamine in two ways, and in a thermostat-like manner [23]. They are believed to act as a dopamine *booster* if they detect too *little* dopamine in the brain (as in depression) but to convert themselves into a dopamine *blocker* if they detect too *much* dopamine in the brain (as in mania). With this two-way action, aripiprazole and cariprazine would therefore be functioning as single-drug *mood stabilizers*, and would promise to be the first genuine single-medication mood stabilizers since lithium.

However, aripiprazole and cariprazine also contain *serotonin*, the main chemical thought to help with depression. Presumably the serotonin somehow supplements the dopamine-blocking action of the drug when the patient is depressed. If so, this makes questionable the common practice of combining the antipsychotic with an antidepressant—most of them these days serotonin-based SSRIs—because a prolonged "double dose" of serotonin could bring on the dangerous and potentially fatal hyper-agitation and bodily function deterioration known as serotonin syndrome [4]. Right now, as shown in **Table 1**, the regulatory

Table 1. Regulatory status of aripiprazole and cariprazine. FDA = U.S. Federal Drug Administration; NIH = U.K. National Institute of Health National Library of Medicine; TGA = Australian Therapeutic Goods Administration.

Drug and Region	Schizophrenia	Acute Mania	Major Depression	Bipolar Maintenance Therapy
Aripiprazole				
U.S.A. (FDA)	YES	YES	YES (with an antidepressant)	YES (with an antidepressant)
U.K. (NIH)	YES	YES	NO	YES (with an antidepressant)
Australia (TGA)	YES	YES	NO	YES (with an antidepressant)
Cariprazine				
U.S.A. (FDA)	YES	YES	NO*	NO
U.K. (NIH)	YES	NO	NO	NO
Australia (TGA)	YES	NO	NO	NO

*Despite claims that cariprazine *is* FDA-approved for major depression (e.g., [33]).

requirements in the U.S., the U.K., and Australia are—inexplicably—that aripiprazole has to be used with an antidepressant whereas cariprazine does not.

A further problem in determining how these two new mood stabilizers works is the inability to *prove* the hypothesized dopaminergic two-way action. The only way to measure brain dopamine is to put the individual into a PET scanner and give him or her mental tasks to solve [24], a procedure hardly possible or ethical for a fully manic or badly depressed bipolar disorder sufferer! This means that the clinician has to simply administer the drug and "hope for the best" while monitoring both depression symptoms and the less often-occurring mania symptoms. This is basically what was done in the clinical trials of aripiprazole and cariprazine.

1.2. Evaluating the Clinical Trials

The present author, a research psychologist and measurement specialist whose brother has had to be hospitalized for bipolar disorder on and off for more than 20 years, therefore decided to evaluate the main placebo-controlled clinical trials of both medications. Specifically reviewed are the trials whose findings were used by the FDA as evidence to support the use of the two drugs in the U.S. Two major limitations, however, should be noted regarding these clinical trials. These are, firstly, the participants' doubtful status with regard to mania in the mania trials and depression in the depression trials, and, secondly, the questionable measures used to assess the effectiveness of the two drugs.

The first limitation is that although the participants in the aripiprazole and cariprazine trials had previously been diagnosed with bipolar disorder using a structured clinical interview, either the DSM-based SCID [25] or the ICD-based MINI [26], the trials themselves were conducted with outpatients who were *not* currently undergoing either a manic episode or a major depressive episode. Also, the discontinuation (dropout) rate during the trials was high, both from the drug-treated group *and* from the placebo-treated group, and it is not clear whether the patients dropped out because the drug they were receiving did not seem to work or whether, on the other hand, it did seem to work and they felt no need to keep attending the clinic for treatment.

The second limitation concerns the *measures* used to evaluate the effectiveness of aripiprazole and cariprazine. The present author, as mentioned earlier, is a specialist in psychological measurement and accordingly was able to examine the measures from a measurement expert's perspective. The results are detailed in the **Appendix** to the present article and the main two problems can be summarized as follows. The measure used to assess *mania*, the Young Mania Rating Scale (YMRS [27]), and the measure used to assess *depression*, the Montgomery-Asberg Depression Rating Scale (MADRS [28]), are *not content-valid with respect to the DSM diagnostic criteria for bipolar disorder*. Total scores on the YMRS and MADRS are used, but total scores ignore necessary versus optional symptoms and thus wrongly count all symptoms equally, relying on the false assumption that total scores measure the severity of, respectively, mania and de-

pression. Total scores, moreover, can be made up in many different ways, many of them omitting the necessary symptoms of mania or depression [29].

To evaluate the clinical trial results, we will have to overlook these faults and take the scores at face value. These scores can be rendered more meaningful by converting them to *percent-of-maximum* scores (see Table 2). The trials for aripiprazole, the older of the two drugs, are discussed first, and the trials for newer one, cariprazine, are discussed second. Both drugs are evaluated first for treating mania and then for treating depression.

2. Aripiprazole Trials

2.1. Aripiprazole and Mania

The main clinical trial of aripiprazole as a treatment for mania was a multi-center, double-blind (neither the clinician nor the patient knew what treatment was being administered) study conducted in the U.S. by Keck *et al.* and

Table 2. Aripiprazole and cariprazine: clinical trial findings for mania and depression. Converted to percentage scores for easy comparison.

Aripiprazole				**Cariprazine**			
Mania				**Mania**			
Keck *et al.* (2009); TGA (2009)				McIntyre *et al.* (2009)			
	Plac. alone	Lith. alone	Arip. alone		Plac. alone	Carip. (3 - 12 mg/day) alone	
YMRS	n = 163	n = 154	n = 153	YMRS	n = 172	n = 281	
Baseline	48	49	48	Baseline	54	53	
3-wk end	33	29	26	3-wk end	37	27	
3-wk change	(−15)	(−20)	(−22)	3-wk change	(−17)	(−26)	
Placebo (%)	–	75	68	Placebo (%)	–	65	
Absolute Advantage (%)	–	+5	+7	Absolute advantage (%)	–	+9	
Depression				**Depression**			
Fava *et al.* (2012)				Earley *et al.* (2019)			
	Plac. + antidep.	Arip. + antidep.			Plac. alone	Carip. (1.5 mg/day) alone	Carip. (3.0 mg/day) alone
MADRS	N = 54	N = 167		MADRS	N = 141	N = 145	N = 164
Baseline	52	51		Baseline	50	51	52
4-wk end	39	37		6-wk end	29	26	26
4-wk change	(−13)	(−14)		6-wk change	(−21)	(−25)	(−26)
Placebo (%)	–	93		Placebo (%)	–	84	81
Absolute advantage (%)	–	+1		Absolute advantage (%)	–	+4	+5

reported in 2009 [16], using the YMRS as the primary effectiveness measure. Unfortunately, as happened with many of the early trials, Keck *et al.* reported only the YMRS *change* scores rather than the mean scores at baseline and at the endpoint, but fortunately the present author was able to locate the mean scores in a lengthy Australian government report on the early trials of aripiprazole [30]. Keck *et al.*'s study was a 3-week trial of aripiprazole alone, lithium (the first mood stabilizer) alone, and placebo alone. The patients had been diagnosed with Bipolar I disorder, which requires at least one lifetime manic episode, and had been hospitalized for the first 2 weeks of the trial for either a manic episode, possibly with psychotic features, *or* for a so-called mixed episode in which the patient had transited to a major depressive episode, also possibly with psychotic features. For some unexplained reason, patients who had not responded to a previous bipolar drug were excluded, thereby omitting treatment-resistant bipolar disorder patients, who were arguably the most important target for the trial.

Following a medication washout period of 2 to 14 days, varying with the patient, from all drugs including antidepressants, patients who apparently had responded to their assigned medication—either aripiprazole, lithium, or placebo—were released from hospital and continued in the trial as *outpatients*, whereas those who apparently did not respond and remained hospitalized were *removed* from the trial (these would be the most seriously suffering patients and their removal would probably bias the results in favor of aripiprazole being effective). Also, the outpatient dropout rate during the trial was very high—just over 50% in all three groups *including* the placebo group (suggesting that for mild symptoms aripiprazole and lithium may be not much different from a placebo). We need only consider the results of the *first* 3 *weeks* (21 days) of drug treatment because the average YMRS scores indicated that a further 9 weeks of treatment produced no further effect.

Keck *et al.*'s 3-week findings are summarized in the upper left panel of **Table 2**. As explained earlier, to make the findings more meaningful, the group-average YMRS scores have been converted into percentage of maximum possible scores (the YMRS has a possible score range of 0-60, so that, for example, a score of 30 is taken to mean that the average participant reported mania severity at 50% of the maximum possible level, in other words, "moderate" mania, or more technically hypomania). Three findings stand out. One is that the average participant was only about "50% manic" at baseline, and with the small standard deviation very few could have been fully manic (and remember that those who *were* fully manic were discontinued). Another is that aripiprazole reduced the symptoms of mania by only an estimated 7% absolute—little better than lithium, the original mood stabilizer, which showed an estimated 5% symptom reduction. Lastly, it is evident that both mood stabilizers were subject to a large placebo effect, in that placebo treatment was approximately 70% as effective as either aripiprazole or lithium in lowering symptoms of mania.

To summarize, aripiprazole was slightly helpful for treating symptoms of moderate mania, though no more helpful than traditional treatment with li-

thium.

2.2. Aripiprazole and Depression

The clinical trial for which aripiprazole was apparently approved by the FDA for treating depression was a series of two identical 8-week double-blind studies conducted by Thase *et al.* in the U.S. and reported in 2008 [17]. We need only evaluate the first of Thase *et al.*'s studies because the findings in the second study were slightly better but cannot overrule the "worst case" findings in the first study. Thase *et al.*'s study is not included in **Table 2** because the study compared aripiprazole alone with placebo alone, whereas, as shown in **Table 1** earlier, aripiprazole has been approved for treating depression only as an *adjunct* to antidepressant medication. Nevertheless, Thase *et al.*'s study is worth reviewing—precisely *because* it omitted the antidepressant, thus simulating the single-drug regulatory status of *cariprazine*, the other new drug reviewed in the present article.

Once again—as has lamentably become common reporting practice—Thase *et al.* reported only the *change* score on the MADRS measure of depression and not the baseline mean score or the endpoint mean score, but it can be reasonably inferred from *Fava et al.'s* study (see below) that the baseline MADRS depression score was about 31, indicating that the average participant in Thase *et al.*'s study was about "52% depressed." Inspection of the graphical data in Thase *et al.*'s study shows that aripiprazole reduced the MADRS depression scores by about 20% absolute and that the placebo reduced them by about 17% absolute. This suggests a net benefit for aripiprazole of just 3% (and that most of its small effect on mild depression is placebic). A major limitation of Thase *et al.*'s study, though, was that people who had *treatment-resistant* depression were excluded, an important point that will be taken up later.

Shown in the lower left panel in **Table 2** are the results of Fava *et al.*'s 2012 double-blind study [18]. In this study, as noted above, aripiprazole, and the placebo, were used in conjunction with an *antidepressant*, which is the combined treatment approved by the FDA. Also, in contrast to Thase *et al.*'s study, treatment-resistant depression patients *were* included. In Fava *et al.*'s study, the participants were *outpatients* who had previously been DSM-diagnosed with major depressive disorder but not with bipolar disorder (an arguably meaningless difference given that the DSM diagnostic criteria for MDD are exactly the same as the DSM diagnostic criteria for MDD in bipolar disorder). In this 8-week trial, the participants were given either aripiprazole or a placebo as an adjunct to the SSRI or SNRI antidepressant that they had been taking for at least 8 weeks prior to the start of the trial (so Fava *et al.*'s trial was *really* about seeing whether the addition of aripiprazole, or perhaps a placebo, would cause the patient's *current antidepressant* to work). Because the participants had already tried the two antidepressants without success and were hopeful for this new medication, the dropout rates in Fava *et al.*'s study were very low, at 14% in the aripiprazole group and an almost identical 10% in the placebo group.

We need to consider only the *first 4 weeks* of 2 mg/day aripiprazole treatment because, after then, the 80% of participants who did not respond to 2 mg/day were shifted to 4 weeks of 5 mg/day while the other 20% remained on 2 mg/day, making the 8-week results impossible to interpret.

The MADRS was the primary measure of depression and again the mean scores have been converted to percentages of the 0 to 60 maximum possible score. There are two findings of note. One is that the participants on average were only about "52% depressed" at the beginning of treatment. Another is that whereas participants in the aripiprazole-plus-antidepressant group showed an absolute 14% reduction in depression symptoms, an almost identical 13% reduction was shown by those in the placebo-plus-antidepressant group—findings indicating that aripiprazole was no more effective than a placebo and therefore did *not* help the antidepressant to work.

To summarize, aripiprazole, even when administered with an antidepressant, proved to be ineffective in alleviating moderate depression.

3. Cariprazine Trials

3.1. Cariprazine and Mania

The clinical trial chosen for the assessment of cariprazine for treating mania was an international multi-center 6-week double-blind trial conducted in the U.S., Russia, India, and four Eastern European countries. The findings from all the trials were combined, averaged, and reported as a single study by McIntyre *et al.* in 2019 [19]. In these 6-week trials for treatment of mania, cariprazine was administered in various doses ranging from 3 mg/day to 12 mg/day, which, it must be noted, is a heavier dose of cariprazine than is used for cariprazine treatment of *depression* (see following section). A separate control group received 6 weeks of placebo treatment. The participants this time were DSM-diagnosed bipolar disorder *in-patients* who had reportedly checked themselves into a hospital or clinic for a recent manic episode, other than their first. (If they checked themselves in, then these people form an immediately suspect sample because most people suffering a manic episode do not realize it or remember it and are very unlikely to think that they need help or hospitalization for it [31]). All patients underwent a 1-week medication washout period, and all other antipsychotic drugs and all antidepressants were prohibited for the duration of the trial. Perhaps because so many different centers were used in the study, dropout rates were not reported, although a previous study of the treatment of mania with cariprazine [31], which is not reviewed here because it lacked a placebo control group, had an alarming 67% dropout rate.

McIntyre *et al.*'s findings are summarized in the upper right panel of **Table 2**. The measure of mania was the YMRS and again the findings have been converted to percentage of maximum possible scores. It can be seen that despite the participants having recently been admitted to hospital for a manic episode, the episode had occurred at least 2 weeks *prior* to the beginning of the trial and had

probably ended for most of them. This meant that the average participant was only just over "50% manic" at baseline (and thus was more likely to be in a state of hypomania). The heavy dose of cariprazine (a rough average would be 7.5 mg/day) was modestly effective in reducing moderate mania from 53% down to 27%, an absolute reduction of 26%, whereas the placebo alone reduced it by an absolute 17%. This implies an absolute 9% advantage for cariprazine, at heavy dosage, over the placebo, and it implies that 65% of cariprazine's effect on mania is itself attributable to a placebo effect.

To summarize, cariprazine appears to be somewhat effective in reducing moderate mania, though at a substantially higher dosage than is used to treat depression. The latter fact, note, reduces its practicality as a single-drug treatment because the clinician would have to change the dose with every mood swing.

3.2. Cariprazine and Depression

Cariprazine was first tested for treating major depressive episodes in bipolar disorder on the basis of a multinational double-blind clinical trial conducted by Durgam *et al.* and reported in 2016 [21] but here we will focus on the more recent double-blind clinical trial conducted by Earley *et al.* and reported in 2019 [22]. This is because the 2016 study tested cariprazine at only 1.5 mg/day whereas the 2019 study tested it at 1.5 mg/day and 3.0 mg/day, the more usual dosage range for depression [14]. Both trials were conducted on *outpatients* who had been previously been DSM-diagnosed with major depressive disorder *without psychotic features*. Rothschild [32], however, has argued strongly against omitting psychotic depression patients, pointing out that approximately 25% of patients in hospital with major depressive order, rising to about 50% of those aged over 60, show psychotic symptoms. Rothschild recommends that cariprazine be tried for these patients, although surprisingly he does not mention the earlier-approved aripiprazole.

The participants in Earley *et al.*'s cariprazine depression trial were required to be suffering a self-reported major depressive episode—other than a psychotic depression episode that they probably would not remember anyway—which, they said, had lasted for at least the previous 4 weeks. Cariprazine was tested alone as a so-called *monotherapy* (whereas aripiprazole, as noted earlier, was tested on depression together with an antidepressant) and the participants underwent a 1- to 2-week washout period from all antidepressants as well as from any *antipsychotics* they may have been taking. Cariprazine was tested during the 6-week trial at two low dosage levels, 1.5 mg/day in one group and 3.0 mg/day in another group. The control group participants were given only a placebo.

Earley *et al.*'s findings are summarized in the lower right panel of **Table 2**. The primary effectiveness measure was again the MADRS depression measure and again the mean scores have been converted to percent of maximum possible scores. Three findings are of interest. Firstly, the participants were on average only about "50% depressed" at the start of the trial, thus indicating moderate

depression. Secondly, cariprazine dosage made no difference, and at either 1.5 mg/day or 3.0 mg/day caused about 26% absolute reduction in depression symptoms, remembering that these were outpatients who presumably had mild but not psychotic depression. Lastly, this finding is undermined by the fact that the placebo did almost as well with about 21% absolute reduction in depression symptoms, implying that about 80% of cariprazine's monotherapy effect on depression is a placebo effect.

In summary, cariprazine administered without a concomitant antidepressant at best offers only a slight advantage over a placebo in reducing moderate depression. It is not known whether cariprazine administered with an antidepressant, as specified by the FDA for aripiprazole, would have made any difference, but the small depression reduction in the aripiprazole-plus-antidepressant study suggests that an antidepressant would *not* have helped.

4. Conclusions

The effectiveness of aripiprazole and cariprazine in treating *moderate* mania, most likely hypomania, and *moderate* depression, was far from encouraging. Aripiprazole produced just 7% greater reduction of mania symptoms than did placebo treatment, and just 1% greater reduction of depression symptoms than did placebo treatment when administered, as is common practice, with an SSRI or SNRI antidepressant. Cariprazine proved to be not much better. At the high dosage level of 3.0 mg/day to 12.0 mg/day, cariprazine produced only 9% greater reduction of mania symptoms than did placebo treatment, and at the typical low dosage of 1.5 to 3.0 mg/day produced just 4% greater reduction of depression symptoms than did placebo treatment. Moreover, as the pharmaceutical industry has long suspected, there is a massive placebo effect associated with these two drugs, especially for depression. Roughly estimated, both drugs' effectiveness on mania, or rather hypomania, is about 65% due to a placebo effect, and on depression, or rather moderate depression, is more than 80% due to a placebo effect. And both drugs carry a risk of side effects whereas placebos do not. These considerations render dubious the FDA's approval of aripiprazole and cariprazine for treating mania and depression in bipolar disorder.

However—and this is a big "however"—even though the two drugs work hardly at all with outpatients suffering with moderate mania or moderate depression, the possibility remains that they might work at the *two extremes*, namely severe mania and severe depression. This would be entirely according to the dopamine hypothesis. The participants with lower-level symptoms of mania or depression may not have had *high* enough dopamine in their system to induce full mania, or may not have had *low* enough dopamine in their system to induce full depression, which in either case would cause the aripiprazole or the cariprazine to "kick in" thermostatically and neutralize the mood. To investigate this possibility, aripiprazole and cariprazine need to be tested on *in-patients* while they are undergoing either a severe manic episode or a severe depressive episode, with

follow-up extended through both episode types for those who experience both mania and depression. Such a trial, however, would be very expensive and also there is the ethical question of whether patients should be given a placebo during a severe episode. Failing such a trial, an alternative might be to solicit psychiatrists' records, on an anonymous basis of course, and do some sort of longitudinal analysis on those.

In any case, it is obvious that we need a unified measure of mania and depression that is briefer and more accurate than the most widely used clinician-rated questionnaire measures, the Young Mania Rating Scale and the Montgomery-Asberg Depression Rating Scale (see the present author's detailed review of each in the **Appendix**). A questionnaire capable of measuring and monitoring both mania and depression is needed because bipolar disorder means *unpredictable mood swings*—including the transition from elation to irritation in manic episodes (despite the present data indicating that a placebo would be almost as effective as the drugs), the complete swing in most cases from the irritation stage of a manic episode to a major depressive episode, and the swing from fairly normal functioning down into a major depressive episode—and it is cumbersome and unnecessary to use separate questionnaires to record them. The present author, a measurement expert, recommends a single questionnaire known as the DEP-6 (see [29]) which includes the manic episode core symptom necessary to diagnose bipolar disorder.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Appendix: Re-Scoring the YMRS and the MADRS

As noted in the present article, the *Young Mania Rating Scale*—simply called the Mania Rating Scale by its originators (see [27]) but now widely referred to as the YMRS—is not an accurate measure of mania, and what has become known as the *Montgomery-Asberg Depression Rating Scale*—its originators did not give it a name (see [28]) but it is now widely referred to as the MADRS—is not an accurate measure of major depression or of the alternatively called but identically symptomatic bipolar depression. In this appendix, the present author shows how to "save" the data from both measures by re-scoring them according to the necessary DSM-5 criteria [5]. (The DSM-5 criteria should be used because criteria in the other leading diagnostic system, the World Health Organization's ICD-10 or forthcoming ICD-11, are vague and inexcusably do not require severe distress or impaired functioning.) The re-scoring method relies on what the present author calls *core symptom theory*.

Core Symptom Theory

This straightforward theory, proposed by the present author [33] and summarized here, states that if the presenting patient does not have the "core"—that is, the *necessary*—symptom or symptoms of a particular disorder, then the patient cannot possibly *have* that disorder. Core symptom theory therefore provides the basis for a much more efficient measure.

Core symptom theory counteracts the erroneous assumptions underlying all multi-symptom measures. The first erroneous assumption is that *all symptoms count equally*. This is wrong because many of the symptoms could have medical causes or be the result of mental disorders other than the focal disorder. The second erroneous assumption is related to the first and is the assumption that the *more* symptoms endorsed, the *worse* the disorder must be. This is wrong because the more symptoms endorsed, the more likely they are to be unrelated symptoms or symptoms not specific to the disorder. The third erroneous assumption is allowing symptoms to count when they are at a subclinical or so-called subsyndromal level. This is wrong because it cannot be assumed that subclinical symptoms will later worsen to a clinical level, or even that they are predictive of this worsening. This "prodromal symptom" notion is readily disproven by the common observation that the onset of biologically-based mental disorders such as bipolar disorder is largely unpredictable—as too is the timing of the mood swings once the disorder takes hold. Lastly, total scores from multi-symptom measures can be arrived at in many different ways, whereas all that matters is that the patient has high scores on the core symptoms.

A key characteristic of core symptom theory is that the necessary symptoms are scored *binary*—present or not present, or yes or no—with regard to the *threshold level of serious dysfunction resulting from that symptom*. There is no treatment effectiveness rationale or recovery monitoring rationale for scoring symptoms on a continuous scale of severity.

Core symptom theory is not so easy to implement, however, because the re-

searcher has to write from scratch items that closely match the DSM-required symptoms in content and also meet the required minimum level of frequency and duration. For the best example of this approach, see First *et al.*'s SCID-5-CV clinical interview measure of bipolar disorder [25]. In the case of the MADRS and the YMRS, however, we cannot change the items or the answer options because the data have already been collected. What we *can* do is select the best items and the best answer options and improve the measure to be more consistent with core symptom theory and the DSM-5.

Furthermore, it should be noted that re-scoring the two measures will not save the *previous studies* that have used the YMRS or the MADRS, such as those reviewed in the present article. This is because the measures for the most part were taken on *outpatients* in the trials who were not actually suffering from a manic episode or a major depressive episode. And although a small proportion of participants might still have been suffering from a current episode and might still qualify as manic or depressed—about 5% judging by the standard deviations—their numbers would be too few to provide meaningful results. The corrections below are therefore aimed at *future* researchers of bipolar disorder who have used *in-patient* samples.

Re-Scoring the YMRS to Measure Mania

The Young Mania Rating Scale [27] is an 11-item measure that has all the problems identified above, along with other major problems. What readers may not realize is that *no actual questions* are provided on the YMRS questionnaire—which means it is far from a standardized measure. Instead, a trained clinician is supposed to conduct an *unstructured interview* lasting from 15 to 30 minutes in which the patient visiting the hospital or clinic is asked to describe his or her condition over the past 48 hours, while the clinician listens for comments and looks for signs of what might be symptoms and then chooses the best fitting answer on each of the YMRS symptom items. Obviously, this procedure will be useless if the patient is still *in* a manic episode and indeed two of the items allow the clinician to record that the patient was impossible to interview or that the interview had to be terminated.

Further de-validating the YMRS is that, as few researchers realize, seven of the 11 symptoms are rated on a 0-to-4 basis whereas the other four are rated on a 0-to-8 basis. This mixed scoring makes total scores on the YMRS completely ambiguous because the total score could be made up in so many different ways. To give an extreme example, a patient could record a total score of 32/60, the sort of mean total score observed in the studies reviewed in the present article, by scoring 8s on the four 0-8 items and zeros on the seven 0-4 items.

The YMRS mania measure consists of the following 11 symptoms: #1—Elevated mood; #2—Increased motor activity-energy; #3—Sexual interest decrease; #4—Sleep decrease; #5—Irritability increase; #6—Increased speech rate; #7—Disordered speech; #8—Thoughts grandiose, paranoid, deluded, or hallucinatory; #9—Disruptive and aggressive behavior; #10—Unkempt or garish appearance; #11—Denial of manic behavior. Eight of the 11 symptoms in the YMRS, however, are

not, according to the DSM-5, required core symptoms of mania. Item #3—Sexual interest decrease, and item #11—Denial of manic behavior, are naive questions to ask if the person is in or is about to be admitted to hospital. Item #4—Sleep decrease, could be the result of depression or a physical disorder. Item #6—Rapid speech, item #7—Disordered speech, and item #8—Delusions and hallucinations, are characteristics of psychosis and are not required symptoms of mania. Item #9—Disruptive and aggressive behavior, could be the result of an impulse disorder, and item #10—Unkempt or garish appearance, could be the result of schizophrenia or simply an unconventional personality. This leaves only three symptoms—items #1, #2, and #5—that are essential to the diagnosis of a manic episode.

Criterion A in the DSM-5 for a manic episode mentions abnormally elevated mood *or* abnormally irritable mood and regards the two states as one symptom, but Frances's [31] stage theory of mania says that they are two different stages and that therefore they should be recorded as two separate symptoms (as is correctly done in the YMRS). The DSM-5 also says that a manic episode must last at least 7 days and a hypomanic episode must last at least 4 days. These duration requirements, however, have recently been disproven [34] such that "several days" is sufficient duration for both (which means that the past 48-hour duration in the YMRS is probably okay). Also, hypomania, the usually milder and non-dysfunctional form of mania, should not be allowed to count, because Bipolar I disorder, the severe form of bipolar disorder that drugs are mainly meant for, requires full mania.

The core symptom recommendations for diagnosing a manic episode, noting that only one is required and that you cannot have both at the same time, are therefore:

(A) Abnormally elevated mood accompanied by hyperactivity, persisting for several days at least, and—by informant report—interfering substantially with performance of normal activities

or

(B) Irritable and impatient mood most of the day, preferably by informant report although self-report might be possible here—a mood which must have been preceded by informant report of symptom A, abnormally elevated mood and hyperactivity—persisting for several days at least, and severe enough that it substantially impairs performance of normal activities

Consistent with core symptom theory, the threshold requirements for frequency, duration, and severity of core symptom A and core symptom B are specified in the wording of the items. This means that each of the two symptoms can be rated binary as yes or no.

Let us now consider what to do if you are "stuck" with YMRS data and wish to save it as best possible.

To detect core symptom A, the researcher should look at the rating on the YMRS for item #1—Elevated mood, to see if it's rated the maximum of 4 (signifying "Euphoric, as indicated by inappropriate laughter, singing"), then look at

the rating on item #2—Increased motor activity-energy, and if that, too, is rated the maximum of 4 (signifying "Motor excitement, as indicated by continuous hyperactivity which cannot be calmed"), it can reasonably be concluded that the patient is present in the *euphoria* stage of mania.

To detect core symptom B, look at the rating on item #5—Irritability, and only if the rating is 6 or 7 (signifying "Frequently irritable, as indicated by unusually curt speech"), then it is likely that the patient is presently manic but has swung to the *impatient irritability* stage. To be *sure* that this is the second stage of a manic episode, the clinician should verify, from informant report if the patient has not been in hospital, that the irritable mood *transitioned from* an abnormally elevated and hyperactive mood. Also, watch out for a score of 8 on item #5—Irritability, because this means that the clinician has rated the patient as "Hostile uncooperative; interview impossible" and, in an obviously wrong move, may have had the patient removed from the data set.

Lastly, researchers should note that other widely used measures of mania have even more problems than the YMRS. The DSM-5 manual recommends only one measure for diagnosing mania: the *Altman Self-Rating Mania Scale*. But this measure is unsuitable because it is self-rated and, as pointed out earlier, a person in the community undergoing a manic episode is most unlikely to be attending a hospital or clinic or even be able to recall the episode. Furthermore, in no way do the five symptoms in the Altman measure correspond with the DSM-5 core symptoms of mania, and the answer scale wrongly records frequency rather than severity. Another widely used measure of mania is the *Mood Disorder Questionnaire*, MSQ, but this, too, is unsuitable because it is self-rated and asks about a lifetime manic episode but not the current manic episode, and includes far too many symptoms beyond the core symptoms. Yet another measure is the *Schedule for Affective Disorders and Schizophrenia*, SADS, which, although consistent with the DSM, has too many symptoms and relies too heavily on patient report rather than clinical observation and informant reports.

Re-Scoring the MADRS to Measure Major Depression

The items that went into the MADRS [28] were appropriately developed based on clinicians' qualitative interviews with depressed patients rather than simply taking the items from previous measures of mania as most measure designers do. The MADRS questionnaire is completed by the clinician, not the patient, and the clinician has to read down the list of answer options for that item and assign the patient's verbal answer to the answer option that seems to fit best. The MADRS also commendably uses verbal answer options that are very much based on how the typical patients would describe their level of the symptom. Whereas this is commendable, the chosen answer option appears merely as a number in the actual data, with the verbal answers ignored, meaning that other researchers cannot see without difficulty how the item was answered.

Moreover, the originators of the MADRS state that if the patient is too ill to provide definite answers—or, it must be added, is not a fluent English speaker—then non-verbal *signs* of the symptom observed during the interview can be

substituted, or else the answers can be sought from one or more *informants* such as family members or friends. However, there is no indication that these stipulations were followed by the depression trial researchers whose studies are reviewed in this article.

The MADRS consists of 10 symptom items rated from 0 to 6, so that the total score can range from 0 to 60. The big problem is that a score of 30/60, the typical mean score in the studies reviewed here, could be obtained in many different ways. Ratings of 0 on five of the symptoms and ratings of 6 on the other five would give a score of 30, but so also would ratings of 3 on all 10 MADRS symptoms, this latter pattern indicating that all symptoms are subclinical or that the clinician is unsure whether the patient has the disorder or not!

Let us therefore turn instead to the DSM-5 criteria for a major depressive episode, which are consistent with the earlier DSM-IV criteria by which the participants in the studies were screened into the depression trial. The DSM major depression diagnosis requires just *one* of the following *two* symptoms, noting that both can be present simultaneously:

(A) Persistent depressed mood, most of the day, nearly every day, lasting for at least 2 weeks, and causing severe distress or substantial dysfunction

or

(B) Marked loss of interest in almost all normally enjoyed activities, most of the day, nearly every day, lasting for at least 2 weeks, and causing severe distress or substantial dysfunction

The wording of A and B, consistent with core symptoms theory, includes minimum requirements—threshold levels—for all three necessary attributes of the symptom: *frequency* ("most of the day, nearly every day"), *duration* ("at least 2 weeks"), and *severity* ("persistent" for depressed mood, and "marked loss" of interest in "almost all" normally enjoyed activities for anhedonia; coupled with "severe distress or substantial dysfunction" resulting from both). Therefore, all the clinician needs to do is to make a *yes or no* rating.

Nevertheless, let us suppose that we are "stuck" with the MADRS data. The MADRS has 10 symptom areas, or actually just nine because the first two are blatant double counting: #1—Apparent sadness; #2—Reported sadness; #3—Inner tension; #4—Reduced sleep; #5—Reduced appetite; #6—Concentration difficulties; #7—Lassitude; #8—Inability to feel; #9—Pessimistic thoughts; #10—Suicidal thoughts.

To detect core symptom A, the researcher should look at the rating on MADRS item #2—*Reported* sadness, and if it is rated at least 4 ("Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances") then the participant can be characterized as having a current major depressive episode.

To detect the alternative core symptom B, the researcher should look at the rating on MADRS item #8—Inability to feel, and, again, if it is rated at least 4 ("Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.") then the patient can be characterized as having a current major depres-

sive episode.

Such is the case, of course, if both symptoms A and B are rated 4 or greater. Actually, there is a good case for requiring both symptoms to be present for diagnosing depression in bipolar disorder. This is because it is the opinion of leading psychiatrists (see, e.g., [12]), and consistent with the DSM-5 manual [5], that the type of depression in bipolar disorder is *melancholic* depression, for which symptom B (anhedonia) is required together with symptom A (persistent depressed mood).

Note that in focusing on ratings of 4 or higher, the clinician is essentially making a binary *yes or no* judgment. Unlike in virtually every mental disorder symptom questionnaire, there are no extra points given for higher-than-threshold ratings.

Lastly, researchers should note (also see [29]) that the two most widely used measures of depression, the *Hamilton Rating Scale for Depression* and the *Beck Depression Inventory*, have precisely the same problems as the MADRS measure. Their symptoms and their verbal rating options do not correspond with the DSM-5, they have too many secondary or ambiguously caused symptoms, and their total scores are meaningless. To boot, whereas these measures were designed originally to be clinician-related, they are too often used today as self-rated measures.