



A Double-Blind Comparison Between Lithium and Third Generation Antipsychotic

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Abstract

Background: While prescription of lithium has been limited in recent years due to its adverse effects and necessity for frequent laboratory tests, second generation antipsychotics (SGAs) are introduced as helpful medications for acute and maintenance treatment of bipolar disorder. To compare lithium with aripiprazole in a group of patients with diagnosis of acute mania was the objective of the present trial.

Methods: A total of 30 male inpatients with diagnosis of bipolar I disorder were entered into a four-week, double-blind study for random assignment to lithium carbonate (800 - 1200 mg/day) or aripiprazole (20 - 30 mg/day) (n =15 in each group). While Manic State Rating Scale (MSRS) was the main outcome measure in the present assessment, other scales such as Bech-Rafaelsen Mania Scale (BRMS), Schedule for Assessment of Insight (SAI) and Clinical Global Impressions-Global Improvement scale (CGI-G) have been used as secondary outcome measures.

Results: At the end of assessment and in comparison with baseline frequency and intensity of symptoms reduced significantly in both groups ($p < 0.05$), improvement was significantly more remarkable by lithium compared with aripiprazole ($p < 0.01$). Also, while CGI-G demonstrated significant improvement by both of them ($p < 0.04$ for aripiprazole and $p < 0.002$ for lithium), BRMS and SAI showed significant amelioration only in the lithium group ($p < 0.001$ and $p < 0.000$, respectively).

Conclusion: Though both aripiprazole and lithium were helpful in the improvement of manic symptoms, treatment with lithium was more advantageous.

Keywords: Bipolar Disorder; Acute Mania; Lithium; Aripiprazole

Introduction

Bipolar and related disorders are separated from the depressive disorders in DSM-5 and placed between the chapters on schizophrenia spectrum and other psychotic disorders and thus enabling depressive disorders to be recognized as a bridge between the two diagnostic classes in terms of symptomatology, family history, and genetics [1]. The bipolar I disorder criteria represent the modern understanding of the classic manic-depressive disorder or affective psychosis described in the nineteenth century, differing from

that classic description only to the extent that neither psychosis nor the lifetime experience of a major depressive episode is a requirement [1]. However, the vast majority of individuals whose symptoms meet the criteria for a fully syndromal manic episode also experience major depressive episodes during the course of their lives [1]. According to ICD -10, in mania, mood is elevated out of keeping with the individual's circumstances and may vary from carefree joviality to almost uncontrollable excitement. Elation is accompanied by increased energy, resulting in over-activity, pres-

sure of speech, and a decreased need for sleep [2]. Normal social inhibitions are lost, attention cannot be sustained, and there is often marked distractibility. Self - esteem is inflated and grandiose or over - optimistic ideas are freely expressed [2]. Perceptual disorders may occur, such as the appreciation of colors as especially vivid (and unusually beautiful), a preoccupation with fine details of surfaces or textures, and subjective hyperacusis. The individual may embark on extravagant and impractical schemes, spend money recklessly, or become aggressive, amorous, or facetious in inappropriate circumstances [2]. Little information exists on specific cultural differences in the expression of bipolar I disorder. One possible explanation for this may be that diagnostic instruments are often translated and applied in different cultures with no trans-cultural validation [2]. In one U.S. study, 12-month prevalence of bipolar I disorder was significantly lower for Afro-Caribbeans than for African Americans or whites. A family history of bipolar disorder is one of the strongest and most consistent risk factors for bipolar disorders [2]. There is an average 10-fold increased risk among adult relatives of individuals with bipolar I and bipolar II disorders. Magnitude of risk increases with degree of kinship. Schizophrenia and bipolar disorder likely share a genetic origin, reflected in familial co-aggregation of schizophrenia and bipolar disorder [2]. The bipolar disorder is often misdiagnosed in particular among outpatients with recurrent depression. Indeed, the unrecognized bipolar disorder is common among depressed outpatients, who are younger, unemployed, single or divorced with a low socio-economic level. Also, the under-diagnosis bipolar disorder seems to be related with the earliest onset age of a depressive episode and more prevalent in depressed patients with suicidal ideation and suicide attempts [3]. Terrible consequences of a manic episode often result from loss of insight, hyperactivity and poor judgment [1]. While the lifetime risk of suicide in individuals with bipolar disorder is estimated to be at least 15 times that of general population, it may account for one-quarter of all completed suicides [1]. Early onset bipolar disorder, in comparison with the later-onset form, shows graver psychosociological consequences, and is characterized, as well, by rapid cycling and increased risks of suicide attempts and substance abuse [4]. Pharmacotherapy is the treatment of choice for acute mania with the primary goal of rapid control of dangerous behavior, aggression and agitation. Presently, along with lithium, the usage of which has been limited in recent years due to its adverse effects and necessity for frequent labora-

tory tests, First Generation Antipsychotics (FGAs), like haloperidol, and Second Generation Antipsychotics (SGAs), like aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone are most widely employed in the treatment of bipolar disorder [4,5]. Among SGAs, aripiprazole, with convincing evidence as a very operative treatment alternative in the controlling of acute manic and mixed episodes of bipolar I disorder [6,7], has been increasingly used, as well, in the maintenance treatment of bipolar disorder and received approval from the U.S. Food and Drug Administration for this indication in 2005 [8]. Furthermore, aripiprazole, as adjunctive to either valproate or lithium, has appeared to be equally safe and effective combinations for the treatment of bipolar disorder [9]. Aripiprazole has been widely used in the management of psychiatric disorders. Dissimilar to other FGAs that mostly have variable degrees of dopamine D2 receptor antagonism, aripiprazole is a partial agonist at dopamine D2 and D3, and serotonin 5-HT1A, and exhibiting antagonistic action at the 5-HT2A and H1 receptors [6,7], which may explain obvious differences in tolerability profiles [10]. Moreover, though the drug is associated with sedation, weight gain and extrapyramidal symptoms (EPS), the incidence of EPS over twelve weeks was not significantly different between aripiprazole (10 mg/day) and placebo [10]. In a comparative study by Keck, *et al.* aripiprazole (15 - 30 mg/day) showed substantial amelioration of acute mania, and the extent of its improvement was comparable with lithium [11]. Also in another study by El-Mallakh, *et al.* [12], aripiprazole monotherapy (15 - 30 mg/day) appeared to be as useful as lithium (900 - 1500 mg/day) for the extended treatment of mixed or manic episodes. Similar standpoint, as well, has been taken by Dhillon [7], who concluded that based on existing guiding principle, aripiprazole is a first-line alternative for the short-term management of mania. Nonetheless, while aripiprazole seems to be a valuable treatment for mania, since comparative studies between aripiprazole and other mood stabilizers are few, so the precise place of aripiprazole in therapy demands further studies [4,13]. Thus, as aripiprazole is the only available third generation antipsychotic now, with the fewest side effects [10], and based on present evidences [4, 7-9], objective of the present assessment was comparing aripiprazole versus lithium in a group of Eastern patient population, who met the diagnosis of acute mania, with their own specific pharmaco-genetic or ethno-psychopharmacologic characteristics.

Method

Thirty male inpatients with diagnosis of bipolar I disorder, according to Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [1], who had been admitted to the hospital due to relapse or new emergence of an episode of acute mania, were entered into a 4-week, double-blind study, for random assignment to aripiprazole or lithium carbonate (Table 1). Informed consent was given by the participant or a legal representative. The study was approved by the ethics committee of the academy. Exclusion criteria were: mixed episode, suicidal ideation, severe instability or aggression, substance abuse, neurological and other severe medical illnesses, previous treatment with antidepressants or long acting antipsychotics (depot). The assessment had been accomplished as a double-blind design, while the patients, staff and assessor were unaware of the prescribed drugs that were packed into identical capsules. While the patients in the first group (n = 15) were given aripiprazole (5 mg uncoated tablets), the cases in the second group (n = 15) were prescribed lithium carbonate (300 mg uncoated tablets). Both of these medicines were given according to practice guidelines and standard titration protocols. Supplier of the aforesaid drugs was the hospital’s pharmacy, and the medications were in generic forms. While prescription of lorazepam, as sedating agent, was permissible in the course of evalu-

ation, no other anticonvulsant or supplementary antipsychotic was allowable during the assessment. Furthermore, except than standard care, no additional psychosocial intervention, like psychotherapy, was acceptable during trial. Manic State Rating Scale (MSRS) was the main outcome measure in the present assessment, which had been scored at baseline and weekly intervals up to the fourth week. The MSRS is an instrument planned for measurement of severity of manic symptoms. The 26 items in this scale are each given a frequency score on a 0 to 5 gauge and an intensity score on a 1 to 5 gauge. Inter-rater reliability for each item has been reported to range from 0.89 to 0.99 [14]. Similarly, severity of manic symptoms, insight, and overall illness severity had been rated using the Bech-Rafaelsen Mania Scale (BRMS, as double-check) [15], Schedule for Assessment of Insight (SAI) [16] and Clinical Global Impressions-Global Improvement scale (CGI-G) [17], respectively. The aforesaid measures had been scored by the same experienced unaware psychiatrist in both groups. Mean modal dosages of aripiprazole and lithium in this trial were 25.83 mg/day (SD=4.93) and 981.81 mg/day (SD = 161.34), respectively. In addition, mean serum level of lithium was 0.8 ± 0.147 mill-equivalents per liter. Mean dosage of adjunctive lorazepam, as well, was 4.5 ± 1.1mg/day for the aripiprazole group and 4.18 ± 0.93 mg/day for the lithium group, with no significant difference (t = 0.746, p < 0.46, 95%CI:-0.57, 1.21).

Groups Demographic Variables	Aripiprazole (N=12)	Lithium (N=11)	t	p	95%CI:
Gender	Male (100%)	Male (100%)	-	-	-
Age (yr.)	30.66 ± 10.37	29.8 ± 12.10	0.211	0.83	-7.57, 9.30
Duration of illness(yr.)	5.86 ± 3.96	7.06 ± 4.02	-0.823	0.41	-4.19, 1.79
Number of prior episodes	3.93 ± 2.20	5.13 ± 3.09	-1.223	0.23	-3.21, 0.81

Table 1: Demographic characteristics of participants.

Statistical analysis

Patients were compared regarding baseline characteristics by means of t tests. Treatment effectiveness, which had been assessed by MSRS, had been analyzed by t test and repeated measures analysis of variance (ANOVA), for intra-group analysis, and Split-plot (mixed) design ANOVA, for between-group analysis. BRMS, SAI and CGI-G, which had been scored at baseline and the end of the 4th week, had been analyzed by t test. Also, Cohen’s effect size (ES), for measurement of the strength of effectiveness, and power of the study (Post-hoc), for evaluation of Type II error, had been analyzed. Statistical significance had been defined as p value ≤0.05. MedCalc

Statistical Software version 15.2 was used as statistical software tool for analysis.

Results

While three patients (20%, n = 3) in the aripiprazole group and four patients (26.66%, n = 4) in the lithium group left the study during the first half of the assessment due to unwillingness or adverse effects of the prescribed drugs, analysis for efficacy was based on data from a comparable number of patients in both groups (z = 0.43; p < 0.66; C I 95% = 0.36, 0.23). The groups were equivalent regarding the baseline characteristics (Table 1). Mean total score

of MSRS improved significantly by both lithium and aripiprazole at the end of 4th week (Table 2) (Figure 1 and 2). This was in spite of the fact that improvement in the aripiprazole group seemed to be faster initially, but it was surpassed by lithium after a short period. With respect to the intensity of manic symptoms, at the end of the trial 41.66% (n = 5) of patients in the aripiprazole group and 63.63% (n = 7) of cases in the lithium group displayed at least 25% decrease in mean total scores of MSRS, in comparison with baseline, and more than 50% improvement was evident in 8.3% (n = 1) and 45.45% (n = 5) of patients of the aforesaid groups, respectively. Between-group analysis displayed significant advantage of lithium, regarding both frequency and intensity, at the end of 3rd and 4th week, respectively (Table 2). Repeated measures analysis of variance (ANOVA) showed significant and non-significant changes in frequency and intensity of MSRS, respectively, in the aripiprazole group, and significant changes in both of the aforesaid variables in the lithium group [F (4, 55) = 2.37 p < 0.05 SS=429.22 MSe = 45.36 and F (4, 50) = 3.75 p < 0.009 SS=1629.14 MSe = 108.48, for frequency, and F (4,55) = 2.08 p < 0.07 SS = 968.77 MSe = 116.18 and F (4,50) = 4.88 p < 0.002 SS = 3264.97 MSe=167.15 for intensity of symptoms in the aripiprazole and lithium groups, respectively]. Split-plot (mixed) design ANOVA also showed significant difference between them [F (9,110) = 2.67 p < 0.007 SS=8562.58 MSe = 356.31 for frequency and, F (9,110) = 2.80 p < 0.005 SS = 8497.93 MSe = 337.74, for intensity of the symptoms, respectively]. Moreover, while mean total score of BRMS showed significant improvement in the lithium group with a reduction around 46.87%, it was not so regarding aripiprazole with an improvement about 26.60%.

The same situation was true regarding SAI, with significant improvement by lithium and insignificant improvement by aripiprazole (Table 3). However, at the end of trial the CGI-G demonstrated significant improvement by aripiprazole and lithium (Table 3). Moreover, since the sample size was not great, the effect size (ES) was analyzed regarding alterations on the MSRS (frequency and intensity) at the end of treatment, which showed large improvement (“d=or > 0.8” or “r=or > 0.3”) with both of them (Table 3). The main reported side effects of aripiprazole in the related group were inner unrest (n = 4, 33.33%), mild stiffness (n = 3, 25%), and sedation (n = 3, 25%). The major adverse effect of lithium in the associated group was tremor (n = 5, 41.66%). Post-hoc power analysis showed a power = 0.31 on behalf of the present assessment, which changed to power = 0.72 in the frame of compromise power analysis.

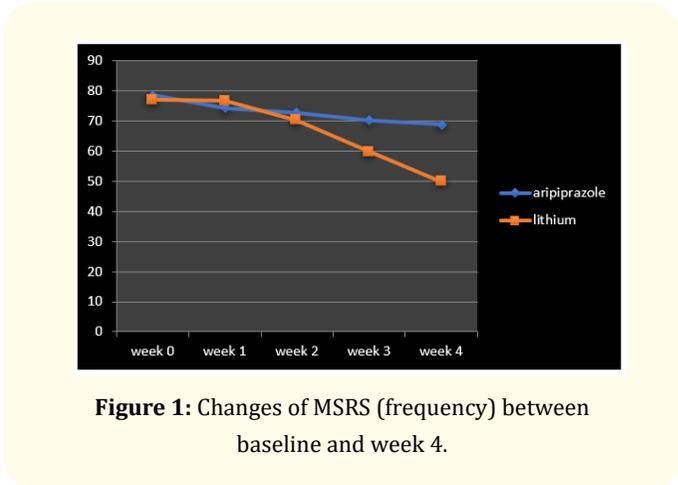


Figure 1: Changes of MSRS (frequency) between baseline and week 4.

Drugs/Outcome Measures	Aripiprazole N=12	Lithium N=11	T	Df	P	95%CI:
MSRS (frequency), week 0	78.51±12.63	77.09±10.68	0.29	21	0.77	-8.77, 11.61
MSRS (frequency), week 1	74.19±8.71	76.75±9.11	-0.68	21	0.49	-10.29, 5.17
MSRS (frequency), week 2	72.79±9.48	70.29±11.17	0.580	21	0.56	-6.46, 11.46
MSRS (frequency), week 3	70.16±10.92	59.87±9.31	2.42	21	0.02	1.45, 19.13
MSRS (frequency), week 4	68.77±9.72	49.93±11.37	4.28	21	0.000	9.69, 27.99
MSRS (intensity), week 0	79.33±9.77	82.18±10.30	-0.68	21	0.50	-11.55, 5.85
MSRS (intensity), week 1	75.70±8.83	80.24±9.83	-1.16	21	0.25	-12.63, 3.55
MSRS (intensity), week 2	74.66±7.25	76.53±8.72	-0.56	21	0.58	-8.80, 5.06
MSRS (intensity), week 3	73.03±10.73	59.97±9.81	3.037	21	0.006	4.12, 22.00
MSRS (intensity), week 4	70.97±10.64	43.12±9.17	6.69	21	0.000	19.20, 36.50

Table 2: Between-group analysis of primary outcome measure at 1st, 2nd, 3rd and 4th week.

Abbreviations: MSRS=Manic State Rating Scale.

Drugs/Outcome Measures	Baseline	Week 4	T	Df	P	95%CI:	Cohen's D	Effect Size R
MSRS (frequency) aripiprazole	78.51 ± 12.63	68.77 ± 9.72	2.117	22	0.04	0.20, 19.28	0.86	0.39
MSRS (frequency) lithium	77.09 ± 10.68	49.93 ± 11.37	5.77	20	0.000	17.35, 36.97	2.46	0.77
MSRS (intensity) aripiprazole	79.33 ± 9.77	70.97 ± 10.64	2.005	22	0.05	-0.29, 17.01	0.81	0.37
MSRS (intensity) lithium	82.18 ± 10.30	43.12 ± 9.17	9.00	20	0.000	28.79, 46.13	5.77	0.94
BRMS aripiprazole	28.42 ± 8.73	20.86 ± 10.11	1.96	22	0.06	-0.44, 15.56	0.73	0.34
BRMS lithium	29.16 ± 9.16	15.49 ± 8.74	3.58	20	0.001	5.71, 21.63	1.52	0.60
SAI aripiprazole	2.75 ± 1.09	3.50 ± 0.83	-1.89	22	0.07	-1.57, 0.07	-0.77	-0.36
SAI lithium	3.10 ± 0.68	7.48 ± 1.13	-11.01	20	0.000	-5.21, -3.55	4.69	-0.92
CGI-G aripiprazole	4.57 ± 1.22	3.69 ± 0.74	2.13	22	0.04	0.03, 1.73	0.87	0.39
CGI-G lithium	4.78 ± 0.92	3.42 ± 0.88	3.54	20	0.002	0.56, 2.16	1.51	0.60

Table 3: Intra-group analysis of different outcome measures between baseline and 4th week, plus effect-size analysis.

Abbreviations: MSRS = Manic State Rating Scale, BRMS =Bech-Rafaelsen Mania Scale, SAI = Schedule for Assessment of Insight, CGI-G = Clinical Global Impressions-Global Improvement scale.

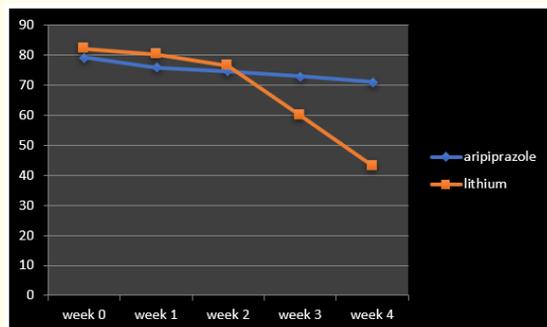


Figure 2: Changes of MSRS (intensity) between baseline and week 4.

Discussion

Although many individuals with bipolar disorder return to a fully functional level between episodes, approximately 30% show severe impairment in work role function [18]. Functional recovery lags substantially behind recovery from symptoms, especially with respect to occupational recovery, resulting in lower socioeconomic status despite equivalent levels of education when compared with the general population. Individuals with bipolar I disorder perform more poorly than healthy individuals on cognitive tests [18]. Cognitive impairments may contribute to vocational and interpersonal difficulties and persist through the lifespan, even during euthymic periods. The lifetime risk of suicide in individuals with bi-

polar disorder is estimated to be at least 15 times that of the general population. In fact, bipolar disorder may account for one-quarter of all completed suicides [18]. A past history of suicide attempt and percent days spent depressed in the past year are associated with greater risk of suicide attempts or completions. Incomplete interepisode recovery is more common when the current episode is accompanied by moodincongruent psychotic features [18]. People with a history of childhood sexual or physical abuse appear to be more at risk, and to have a worse prognosis [18]. Long-term functional prognosis (work, family, etc.) (particularly in untreated patients) is almost as poor as in schizophrenia. There is an overall increase in premature mortality, only partially explained by a suicide rate of 10% [19]. Currently, no convincing evidence suggests that atypical antipsychotic medications are superior to typical medications for the treatment of psychosis. However, atypical antipsychotic medications may be more acceptable due to fewer symptomatic adverse effects in the short term. While little evidence is available to support the superiority of one atypical antipsychotic medication over another, side effect profiles are different for different medications. For example, while treatment with olanzapine, risperidone and clozapine is often associated with weight gain, aripiprazole is not associated with increased prolactin or with dyslipidaemia. In addition, whereas adolescents may respond better to standard-dose as opposed to lower-dose risperidone, with respect to aripiprazole and ziprasidone, lower doses may be equally effective. Consequently, uniform ways of reporting, in future studies, will be an indispensable stratagem for achievement of inclusive consensus

among researchers [13,20]. Back to our study, while in intra-group analysis aripiprazole and lithium were statistically and significantly useful in amelioration of manic symptoms, lithium was significantly more effective than aripiprazole in between-group analysis after four weeks, which was clearly evident at the end of 3rd week, too. Such a state of affairs is somewhat consistent with the insignificant improvement of intensity of symptoms by aripiprazole. The same inference, as well, is valid regarding final outcome of secondary measures like BRMS and SAI, despite the fact that it was not so with regard to CGI-G, which was significantly improved in both groups. Perhaps it could be expressed that while improvement in the aripiprazole group was statistically significant, from a pragmatic perspective, it was more evident in the lithium group. Hence, it is obvious that such a finding, which could not be in complete agreement with the findings of Keck, *et al.* and El-Mallakh, *et al.* who had found aripiprazole comparable to lithium for management of acute mania [11,12], make it hard to determine which one is better than other. Similarly, it is not in harmony with Dhillon, who concluded that based on existing guiding principle, aripiprazole is a first-line alternative for the short-term management of mania [7,10], and as a first-line or second-line alternative for stopping the relapse of mood episodes in the course of longer-term treatment [7,21,22]; although the report showed that additional evaluations for comparing aripiprazole with other medications, including SGAs, are required and would aid to conclusively determine the position of aripiprazole in relation to other drugs [23]. Furthermore, the existing evidence does not support the effectiveness of aripiprazole for the management of bipolar depression and stopping its relapse [23]. a capability that is conceivable by lithium [24]. Similarly, while some believe that, based on an insufficient amount of direct comparisons, antipsychotic drugs (haloperidol or SGAs) may have shown greater efficacy or faster action than mood stabilizers like lithium, valproate and carbamazepine [20], others believe that there are essentially insufficient studies comparing lithium with SGAs [5]. Moreover, in the study of El-Mallakh, *et al.* of the 66 patients who entered the study, only 20 patients completed the entire phase, and based on 60% drop-out rate of the patient population, their trial could not be supposed, statistically, powered enough for precise clinical judgment [12]. Similarly, while recently in the Europe, oral aripiprazole was approved for the treatment of moderate to severe manic episodes in adolescents with bipolar I disorder, another time due to high drop-out ratio, effectiveness during long-term treatment (over 30 weeks) could not be verified

[10]. Additional different outcomes are available regarding comparing lithium with other anti-manic agents. For example in a double-blind study on forty female inpatients meeting DSM-IV-TR criteria for acute mania, while both olanzapine and lithium were found to be significantly helpful in the improvement of manic symptoms, lithium was significantly more effective than olanzapine [25]. Also in another study, while both lithium and valproate were effective for improvement of manic symptoms, lithium was significantly more effective than valproate [26]. Likewise, though the results of several assessments strongly show that many anti-manic drugs are significantly more useful than placebo, their comparable effect sizes and overlapping confident intervals make it hard to determine that which one is better than other. In addition, modern medical practice, generally influenced by additional factors like cost and time, regularly use a combination of anti-manic agents to bring mania under control as fast as possible – especially combinations of antipsychotics and mood stabilizers [20]. Though the findings of the present assessment are not in agreement with aforementioned surveys, employment of various outcome measures, different techniques of analysis, dissimilar durations of treatment, various sample sizes, different treatment dosages, and unlike patient cohorts (sex, age, duration of illness, number of episodes, smoking state and pharmacological as well as other pre-treatments) should not be ignored, due to their possible influence on the results of the individual investigations. Additionally, it should not be disregarded that possible pharmaco-genetic or ethno-psychopharmacologic differences, between Western and Eastern people, may have influenced the outcome of the present assessment. But, in spite of contradictory results, when we noticed the similar findings regarding superiority of lithium over other SGAs [25] or mood stabilizers [26], we can conclude that the results of the present assessment regarding stronger effect of lithium on frequency and intensity of symptoms, assisted in restating important clinical fact, which could have been omitted due to hurried inferences. Our findings pertaining to adverse effects, as well, were not precisely similar to the result of a former study by El-Mallakh, *et al.* [12], who had found nasopharyngitis, headache and somnolence in their samples due to aripiprazole. Although the fear of lithium toxicity and its narrow therapeutic index may encourage a lot of clinicians to choose more innocent medications similar to SGAs, availability of precise laboratory checking of serum level of lithium and judicious employment of standard physical and laboratory checkups may encourage doctors to modify their perspective regarding lithium.

Small sample size, short duration of evaluation, gender-based sampling, and exclusion of mixed episodes were among the weaknesses of this trial.

Conclusion

Though both aripiprazole and lithium were helpful for improvement of manic symptoms, treatment with lithium was more advantageous.

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Bibliography

- American Psychiatric Association (APA). "Diagnostic and Statistical Manual of Mental Disorders". 5th ed. Washington, DC: American Psychiatric Association (2013): 123-132.
- Neel Burton, Psychiatry, 2nd Edition, John Wiley and Sons Ltd, Oxford, UK (2010): 89-120.
- Bouchra O., et al. "Screening of the unrecognized bipolar disorders among outpatients with recurrent depressive disorder: a cross-sectional study in psychiatric hospital in Morocco". *Pan African Medical Journal* 27 (2017): 247.
- Brown R., et al. "Aripiprazole alone or in combination for acute mania". *The Cochrane Database of Systematic Reviews* 12 (2013): CD005000.
- Tohen M and Vieta E. "Antipsychotic agents in the treatment of bipolar mania". *Bipolar Disord* 11.2 (2009): 45-54.
- Sayyaparaju KK., et al. "When to start aripiprazole therapy in patients with bipolar mania". *Neuropsychiatric Disease and Treatment* 10 (2014): 459-470.
- Dhillon S. "Aripiprazole: a review of its use in the management of mania in adults with bipolar I". *Disorder Drugs* 72.1 (2012): 133-162.
- Tsai AC., et al. "Aripiprazole in the maintenance treatment of bipolar disorder: a critical review of the evidence and its dissemination into the scientific literature". *PLOS Medicine* 8.5 (2011): 100-114.
- Vieta E., et al. "Assessment of safety, tolerability and effectiveness of adjunctive aripiprazole to lithium/valproate in bipolar mania: a 46-week, open-label extension following a 6-week double-blind study". *Current Medical Research and Opinion* 26.6 (2010): 1485-1496.
- McKeage K. "Aripiprazole: a review of its use in the treatment of manic episodes in adolescents with bipolar I disorder". *CNS Drugs* 28.2 (2014): 171-183.
- Keck PE., et al. "Aripiprazole monotherapy in the treatment of acute bipolar I mania: a randomized, double-blind, placebo- and lithium-controlled study". *Journal of Affective Disorders* 112.1-3 (2009): 36-49.
- El-Mallakh RS., et al. "A 40-week double-blind aripiprazole versus lithium follow-up of a 12-week acute phase study (total 52 weeks) in bipolar I disorder". *Journal of Affective Disorders* 136.3 (2012): 258-266.
- Kumar A., et al. "Atypical antipsychotics for psychosis in adolescents". *The Cochrane Database of Systematic Reviews* 15.10 (2013): CD009582.
- Beigel A., et al. "The Manic-State Rating Scale: Scale Construction, Reliability, and Validity". *Archives of General Psychiatry* 25 (1971): 256-262.
- Bech P., et al. "The Bech-Rafaelsen Mania Scale and the Hamilton Depression Scale". *Acta Psychiatrica Scandinavica* 59.4 (1979): 420-430.
- David AS. "Insight and Psychosis". *British Journal of Psychiatry* 156 (1990): 798-808.
- Clinical Global Impressions, "ECDEU Assessment manual for psychopharmacology, Guy W, ed, Rockville: U.S Department of Health, Education, and Welfare, DHEW Publication NO. (ADM) (1976): 76-338.
- Neel Burton, Psychiatry, 2nd Edition, John Wiley and Sons Ltd, Oxford, UK (2010): 89-120.
- Cornelius Katona., et al. "Psychiatry at a Glance, 5th Edition". John Wiley and Sons Ltd, Oxford, UK (); 24-25.
- Yildiz A., et al. "Efficacy of Antimanic Treatments: Meta-analysis of Randomized, Controlled Trials". *Neuropsychopharmacology* 36.2 (2011): 375-389.

21. Yatham LN, *et al.* "Efficacy of aripiprazole versus placebo as adjuncts to lithium or valproate in relapse prevention of manic or mixed episodes in bipolar I patients stratified by index manic or mixed episode". *Journal of Affective Disorders* 147.1-3 (2013): 365-372.
22. McIntyre RS. "Aripiprazole for the maintenance treatment of bipolar I disorder: A review". *Clinical Therapeutics* 32.1 (2010): 33-38.
23. Yatham LN. "A clinical review of aripiprazole in bipolar depression and maintenance therapy of bipolar disorder". *Journal of Affective Disorders* 128.1 (2011): 21-28.
24. Harrison P, *et al.* "Lecture Notes: Psychiatry, 10th Edition". Wiley-Blackwell, United Kingdom (2010): 100-101.
25. Shoja Shafti S. "Olanzapine vs. lithium in management of acute mania". *Journal of Affective Disorders* 122 (2010): 273-276.
26. Shoja Shafti S and Shahveisi B. "Comparison Between Lithium and Valproate in the Treatment of Acute Mania". *Journal of Clinical Psychopharmacology* 28.6 (2008): 718-720.

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