Management of Acute Mania: Comparison of Treatment Outcomes for Aripiprazole vs Lithium

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Abstract

Objective: While prescription of lithium has been limited in recent years due to adverse effects and necessity of frequent laboratory tests, second generation antipsychotics are introduced as helpful medications for acute and maintenance treatment of bipolar disorder. Comparing lithium with aripiprazole in a group of patients with acute mania was the purpose of the present assessment.

Methods: Thirty 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: While 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, in comparison with aripiprazole ($p <0.01$). Though CGI-G demonstrated significant improvement by both of them ($p < 0.04$ for aripiprazole & $p < 0.002$ for lithium), BRMS and SAI showed significant amelioration only by lithium ($p<0.001$ & $p<0.000$, respectively).

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

Keywords: Bipolar Disorder; Acute Mania; Lithium; Aripiprazole

Introduction

Bipolar disorders are separated from the depressive disorders in DSM-5 and had been placed between the chapters on schizophrenia spectrum and other psychotic disorders and depressive disorders in recognition of their place as a bridge between the two diagnostic classes in terms of symptomatology, family history, and genetics [1]. According to ICD -10, in mania, mood is oddly elevated and may vary from carefree joviality to almost uncontrollable excitement. Elation is accompanied by increased energy, resulting in over-activity, pressure 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, as well, is inflated and grandiose. The bipolar disorder is often misdiagnosed in particular among outpatients with recurrent depression. 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. Early onset bipolar disorder, in comparison with the later-onset form, shows graver psychosocial consequences, and is characterized, as well, by rapid cycling and increased risks of suicide attempts and substance abuse [4]. Although many individuals with bipolar disorder return to a fully functional level between episodes, approximately 30% show severe impairment in occupational tasks. Functional recovery lags substantially behind recovery from symptoms, especially with respect to work-related retrieval, 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. Cognitive impairments may contribute to vocational and interpersonal difficulties and persist through the lifespan, even during euthymic periods. Moreover, people with a history of childhood sexual or physical abuse appear to be more at risk, and to have a worse prognosis.

In general, long-term functional prognosis, particularly in untreated patients, is almost as poor as in schizophrenia [5]. Pharmacotherapy is the treatment of choice for acute mania with the primary goal of rapid control of dangerous behavior, aggression and agitation. Todays, along with lithium, the usage of which has been limited in recent years due to its adverse effects and necessity for frequent laboratory 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 [4,6]. 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 [7,8], 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 [9]. Aripiprazole has been widely used in the management of psychiatric disorders [10].

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 [7,8], which may explain obvious differences in tolerability profiles [11]. 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. In a comparative study by Keck, *et al.* [12], aripiprazole (15-30 mg/day) showed substantial amelioration of acute mania, and the extent of its improvement was comparable with lithium [12].

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 maintenance treatment of mixed or manic episodes [13]. Similar view, as well, has been assumed by Dhillon, who had concluded that based on existing data, 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 [4,14]. So, objective of the present assessment was comparing aripiprazole vs. lithium in a group of Eastern patient population, who met the diagnosis of acute mania.

Methods

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). While the human studies in this work were carried out in accord with the 'Declaration of Helsinki and Ethical Principles for Medical Research Involving Human Subjects', the participants were informed regarding the procedure, and a printed permission was received from those who were attentive to participate in the assessment. Exclusion criteria included: mixed episode, suicidal ideation, severe instability or aggression, substance abuse, neurological and other severe medical illnesses, previous treatment with antidepressants or injecting long acting antipsychotics. The assessment had been accomplished as a double-blind design, while the patients, staff and assessor were unaware of the prescribed medications, which were packed into similar capsules.

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

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 formulas. While prescription of lorazepam, as sedating agent, was permissible in the course of evaluation, 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 evaluation, 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 of '0-5' and an intensity score of '1-5'. Inter-rater reliability for each item has been reported to range between 0.89-0.99 [15]. Similarly, severity of manic symptoms, insight, and overall illness severity had been rated by Bech-Rafaelsen Mania Scale (BRMS, as double-check) [16], Schedule for Assessment of Insight (SAI) [17] and Clinical Global Impressions-Global Improvement scale (CGI-G) [18], in turn. The aforesaid measures had been scored by the same experienced unaware psychiatrist in both groups. In addition, mean modal doses of aripiprazole and lithium in the current trial were 25.83 mg/day (SD=4.93) and 981.81 mg/day (SD=161.34), respectively. Moreover, mean serum level of lithium was around 0.8 ± 0.147 mill-equivalents per liter. Mean dosage of adjunctive lorazepam, as well, was 4.5 ± 1.11 mg/day for the aripiprazole group and 4.18 ± 0.93 mg/day for the lithium group, with no significant difference with respect to dosages (t=0.746, p<0.46, 95%CI:-0.57, 1.21).

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 analogous number of patients in both groups (z = 0.43; p<0.66; C I 95% = 0.36, 0.23). The groups were comparable regarding the baseline characteristics (Table 1). According to the outcomes, mean total score of MSRS improved significantly by lithium and aripiprazole at the end of the 4th week (Table 2) (Figure 1 & 2). This was in spite of the fact that improvement in the aripiprazole group appeared 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 exhibited at least 25% decrease in mean total scores of MSRS, in comparison with starting point, and more than 50% improvement was evident in 8.3% (n=1) and 45.45% (n=5) of patients of the aforesaid groups, respectively.

Drugs/Outcome measures	Aripiprazole n=12	Lithium n=11	t	df	p	95%CI:	Cohen's d	Effect size r
MSRS (frequency), week 0	78.51±12.63	77.09±10.68	0.29	21	0.77	-8.77, 11.61	0.86	0.39
MSRS (frequency), week 1	74.19±8.71	76.75±9.11	-0.68	21	0.49	-10.29, 5.17	2.46	0.77
MSRS (frequency), week 2	72.79±9.48	70.29±11.17	0.58	21	0.56	-6.46, 11.46	0.81	0.37
MSRS (frequency), week 3	70.16±10.92	59.87±9.31	2.42	21	0.02	1.45, 19.13	5.77	0.94
MSRS (frequency), week 4	68.77±9.72	49.93±11.37	4.28	21	0	9.69, 27.99	0.73	0.34
MSRS (intensity), week 0	79.33±9.77	82.18±10.30	-0.68	21	0.5	-11.55, 5.85	1.52	0.6
MSRS (intensity), week 1	75.70±8.83	80.24±9.83	-1.16	21	0.25	-12.63, 3.55	-0.77	-0.36
MSRS (intensity), week 2	74.66±7.25	76.53±8.72	-0.56	21	0.58	-8.80, 5.06	4.69	-0.92
MSRS (intensity), week 3	73.03±10.73	59.97±9.81	3.037	21	0.006	4.12, 22.00	0.87	0.39
MSRS (intensity), week 4	70.97±10.64	43.12±9.17	6.69	21	0	19.20, 36.50	1.51	0.6

MSRS=Manic State Rating Scale

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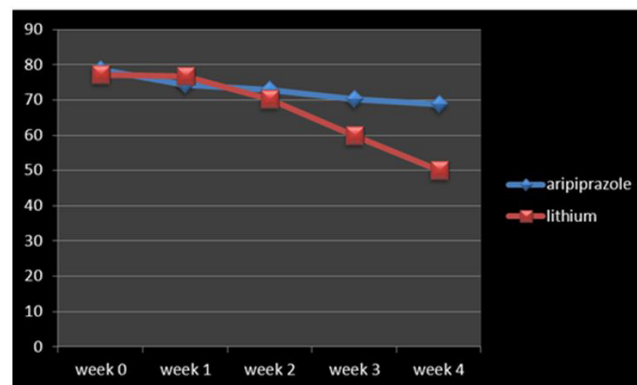

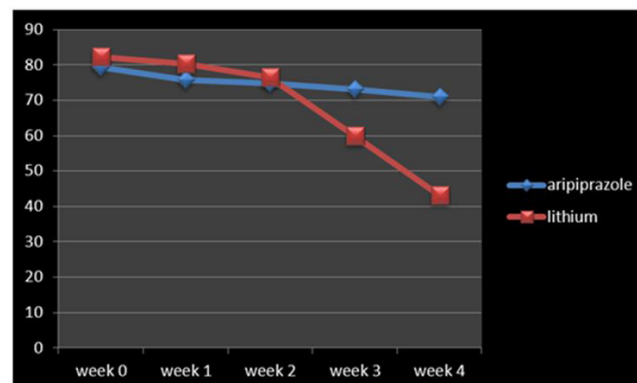**Figure 1:** Changes of MSRS (frequency) between baseline and week 4

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

Between-group analysis presented significant advantage on behalf of lithium, regarding frequency and intensity of symptoms, at the end of the 3rd and 4th week (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 concerning aripiprazole, with an improvement around 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 assessment the CGI-G demonstrated significant improvement by both aripiprazole and lithium. 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 medications. The highest reported side effects of aripiprazole included inner unrest (n = 4, 33.33%), mild stiffness (n = 3, 25%), and sedation (n = 3, 25%). The major adverse effect of lithium involved 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.

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	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	20	0	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	0.6
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	-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	0.6

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

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

Discussion

Though at this time no convincing evidence suggests that atypical antipsychotics are superior to typical antipsychotics for treatment of psychosis, atypical antipsychotic medications may be more acceptable due to fewer symptomatic adverse effects in the short term. On the other hand, while little evidence is available to support the superiority of one atypical antipsychotic medication over another, side effect profiles are different for different drugs. For example, though treatment with olanzapine, risperidone and clozapine is often associated with weight gain, aripiprazole is not associated with increased prolactin or with dyslipidaemia. Also, while 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. So, in future studies, identical techniques of assessment, will be an indispensable stratagem for final achievement of inclusive consensus among different researchers [15,19].

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 evidently manifested 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, whilst it was not so with regard to CGI-G, which was significantly improved by both medications. Perhaps it could be stated that though improvement by aripiprazole was statistically significant, from a pragmatic perspective, it was more evident by lithium. Hence, it is obvious that such a finding, which could not be in complete agreement with the findings of Keck *et al.* [12] and El- Mallakh, *et al.* [13], who had found aripiprazole comparable to lithium for management of acute mania make it hard to determine that which one is better than other.

Similarly, it is not in harmony with the assumptions of Dhillon , who had concluded that based on the existing data aripiprazole is a first-line alternative for the short-term management of mania, and as a first-line or second-line alternative for stopping the relapse of mood episodes in the course of longer-term management [9,20,21]; though he had stated that additional evaluations for comparing aripiprazole with other SGAs, are required and would aid to conclusively determine the position of aripiprazole in

relation to other medications [22]. Similarly, while based on insufficient amount of direct comparisons, some scholars believe that antipsychotic drugs (haloperidol or SGAs) may have shown greater efficacy or faster action than mood stabilizers like lithium, valproate and carbamazepine, others believe that there is not essentially enough studies comparing lithium with SGAs. Moreover, in the study of El-Mallakh, *et al.* [13], and Of the 66 patients who entered the study, only 20 patients completed the entire phase, and so due to high drop-out ratio, their trial could not be supposed flawless for exact clinical judgment [23].

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, again, due to high drop-out ratio, its effectiveness during long-term treatment could not be verified. 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 [24]. Also in another study, while both lithium and valproate were effective for improvement of manic symptoms, lithium was significantly more effective than valproate [25]. Anyhow, 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.

Furthermore, modern medical practice, which is generally influenced by additional factors like cost and time, regularly use a combination of anti-manic agents, especially combinations of antipsychotics and mood stabilizers, to control mania as fast as possible. Though the findings of the present assessment are not in agreement with the said studies, usage of different outcome measures, different techniques of analysis, unalike 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 separate inquiries. Additionally, it should not be ignored 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 notice the similar findings regarding superiority of lithium over other SGAs or mood stabilizers, we can conclude that the results of the present assessment regarding stronger effect of lithium on frequency and intensity of symptoms, is nothing except than restating of an important clinical fact, which could have been overlooked due to biased analyses. Our conclusions with respect to adverse effects, as well, were not precisely similar to the outcomes of El-Mallakh, *et al.* [13], who had found nasopharyngitis, headache and somnolence caused by 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 levels 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 the present trial.

Conclusion

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

Acknowledgment

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