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Is Aristada (Aripiprazole Lauroxil) a Safe and Effective Treatment For Schizophrenia In Adult Patients?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences- Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not “Is Aristada (aripiprazole lauroxil) a safe and effective treatment for schizophrenia in adult patients?”

STUDY DESIGN: Review of three randomized controlled studies. All three trials were conducted between 2014 and 2015.

DATA SOURCES: One randomized, controlled trial and two randomized, controlled, double-blind trials found via Cochrane Library and PubMed.

OUTCOMES MEASURED: The outcomes that were measured include adverse events (pain at injection site, insomnia, headache, toothache, abdominal discomfort, constipation, diarrhea, akathisia, back pain, dyskinesia, dystonia, nasopharyngitis) measured by vital signs, physical examination, and clinical laboratory tests. Improvement in psychotic symptoms measured by PANSS (Positive and Negative Syndrome Scale) and CGI-I scale (Clinical Global Impressions-Improvement Scale). Also, effect on agitation and hostility measured by PANSS, Personal and Social Performance Scale, and disturbing and aggressive behavior.

RESULTS: The three randomized, controlled trials showed that the use of aripiprazole lauroxil was effective at reducing symptoms of schizophrenia including hostility and agitation, based on PANSS, CGI-I, and PSP scores. Results in reducing symptoms were seen as early as 8 days after initial administration in some cases. Aripiprazole lauroxil was also found to be safe in the trials with, only a limited number of mild to moderate adverse events occurring among certain participants in the studies, mostly injection site pain.

CONCLUSIONS: Based on these three trials, Aristada (aripiprazole lauroxil) is a safe and effective treatment option for schizophrenia in adult patients.

KEY WORDS: Aripiprazole lauroxil, schizophrenia

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INTRODUCTION

Schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels and behaves.⁴ Aripiprazole lauroxil is a new, novel LAI atypical antipsychotic that may be used for the treatment of schizophrenia. This paper evaluates three randomized, controlled trials comparing the effectiveness and safety of Aristada (aripiprazole lauroxil) in treating the symptoms of schizophrenia in adult patients.

Schizophrenia is relevant to patients and Physician Assistant practice due to its prevalence, cost to patients, and the number of health care visits per year from it. Schizophrenia affects 7.2 individuals per 1,000 living in the United States and about 100,000 people living in the country will be diagnosed this year.⁵ The overall United States health care cost of schizophrenia was estimated to be \$62.7 billion in 2002, with \$5 billion of that for drugs alone.⁵ The 12 month health care use rate is 60% of adult patients with schizophrenia.⁴ Due to all of these reasons, it is imperative for Physician Assistants to be aware of schizophrenia and the burden that it places on patients who are affected by it.

The exact etiology of schizophrenia is unknown. It is a complex condition that is increasingly being recognized as a collection of different disorders. Genetic influence has been found to play a role. It is also being viewed from a developmental perspective.⁴ Symptoms of schizophrenia are classified as “positive” or “negative”. The positive symptoms include hallucinations, delusions, and thought disorders.⁴ The negative symptoms include lack of motivation to accomplish goals, blunted affect or emotion, and lack of desire to form social relationships.⁴ There is currently no curative treatment for schizophrenia, and its treatment is aimed at symptom control.

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The typical first line treatment for schizophrenic patients is with atypical antipsychotics or the older “typical” antipsychotics. Atypical antipsychotics include Risperidone, Quetiapine, Olanzapine, Clozapine, Asenapine, and Ziprasidone. “Typical” antipsychotics include Chlorpromazine, Fluphenazine, Haloperidol, and Perphenazine. Other treatment options include psychosocial support, cognitive behavioral therapy, rehabilitation, and family support. Patients may choose to utilize a combination of treatment options that work most effectively for control of their symptoms. Due to lack of efficacy and contraindications to other treatment options, Aristada (aripiprazole lauroxil) may be used as an effective treatment for schizophrenia in adult patients.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not “Is Aristada (aripiprazole lauroxil) a safe and effective treatment for schizophrenia in adult patients?”

METHODS

The criteria used for selection of studies in this review included a population of adult patients between the ages of 18 and 70 who have been diagnosed with schizophrenia and are experiencing an acute exacerbation. The intervention was the administration of aripiprazole lauroxil 441 mg IM or 882 mg IM. Comparisons were made between the treatment groups receiving aripiprazole lauroxil to the experimental groups who received a placebo. Outcomes measured included adverse events (pain at injection site, insomnia, headache, toothache, abdominal discomfort, constipation, diarrhea, akathisia, back pain, dyskinesia, dystonia, and nasopharyngitis), improvement in psychotic symptoms, and effect on agitation and hostility. The studies included one randomized, controlled trial and two randomized, controlled, double-blind

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trials that evaluated aripiprazole lauroxil as an effective treatment for schizophrenia in adult patients.

The key words used when searching for the articles included “schizophrenia” and “aripiprazole lauroxil”. All of the chosen articles were published in English and in peer-reviewed journals. The articles chosen were researched by the author and selected after being searched via Cochrane Library and PubMed. The articles were selected based on relevance to the clinical question, the types of studies, and whether or not the outcomes mattered to patients. The inclusion criteria included patients aged 18 and up diagnosed with schizophrenia by DSM-IV-TR criteria, and studies that were randomized, controlled trials evaluating efficacy and safety of aripiprazole lauroxil. The exclusion criteria included studies with patients under the age of 18 years, and studies that did not provide information on efficacy of aripiprazole lauroxil in treating schizophrenia. The statistics reported or used include p-values and percentages. Table 1 displays demographics and characteristics of included studies.

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Table 1: Demographics & Characteristics of included studies:

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Turncliff ¹ (2014)	RCT	46	18-55 yrs	-Aged 18 to 55 yrs with chronic schizophrenia or schizoaffective disorder -BMI of 18 to 40 kg/m ² -On stable med >2 months -Previous aripiprazole use	-Suicidal behavior/ideation -Any unstable medical illness -Use of aripiprazole within 60 days of screening -Substance abuse within 3 months of screening -Women pregnant or breastfeeding -Corrected QT interval	3	Aripiprazole lauroxil 441 mg IM (Deltoid vs. Gluteal administration)
Meltzer ² (2015)	Double blind RCT	623	18-70 yrs	-Aged 18-70 with schizophrenia and experiencing an acute exacerbation -PANSS score of 70 to 120 -Outpatient >3 months	-Significant medical illness -Women pregnant or breastfeeding -Substance dependence -Previous inadequate response to aripiprazole -Comorbid cognitive disorder	262	Aripiprazole lauroxil 441 mg & 882 mg gluteal IM
Citrome ³ (2015)	Double blind RCT	622	18-70 yrs	-Aged 18-70 yrs with schizophrenia -Currently experiencing acute exacerbation -Outpatient for more than 3 months -PANSS total score of 70 to 120	-Received long-acting antipsychotics and agents that would effect metabolism of aripiprazole lauroxil - Currently hospitalized involuntarily -Use of MAO inhibitors, lithium, mood stabilizers	27	Aripiprazole lauroxil 441 mg & 882 mg IM

OUTCOMES MEASURED

The outcomes measured in the trials were all patient-oriented evidence that matters. In Turncliff et al study, the outcomes measured were safety evaluations for adverse events and injection site reactions that were measured using clinical laboratory testing, physical examination, vital signs, and 12-lead electrocardiogram.¹ Blood samples were collected at pre-specified times to determine plasma concentrations of the drug in the patients after IM dosing.¹ The C-SSRS was used at screening, baseline, and during the trial to evaluate patients for suicidal ideation, and the ESRS was used to evaluate patients for extrapyramidal symptoms.¹ In Meltzer et al study, the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions-Severity of Illness scale (CGI-S) were used, along with the Clinical Global Impressions-Improvement scale (CGI-I) to measure efficacy of aripiprazole lauroxil to improve psychotic symptoms.² Safety was also evaluated in Meltzer et al study, through monitoring adverse events measured by vital signs, physical examination, ECG findings, injection site reaction evaluation, and lab tests.² In Citrome et al study, the effect of aripiprazole lauroxil on agitation and hostility was measured using PANSS and the Personal and Social Performance (PSP) scale.³ The PANSS Hostility item P7 and the PANSS-EC (excited component) were components of PANSS used to determine the effects on agitation and hostility as well.

RESULTS

The three randomized, controlled trials in this EBM review all demonstrated statistical results based on their respective studies.

In the Turncliff et al study, 38 (82.6%) of patients experienced at least one treatment-emergent adverse event. All of these adverse events were mild or moderate in intensity.¹ The

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incidence of adverse events was higher in the deltoid administration group. The most common adverse event was injection site pain in 20 (43.5%) subjects.¹ The most common systemic adverse events were headache (13.0%), insomnia (10.9%), and toothache (10.9%).¹ The adverse events of dyskinesia and dystonia each occurred in 3 subjects (13.6%) in the deltoid group, but not the gluteal group. No severe adverse events occurred during the study and no discontinuations due to adverse events occurred.¹ No clinically significant effects of aripiprazole lauroxil on vital signs, physical examination, or 12-lead electrocardiogram were found.¹ Changes from clinical laboratory tests were small, with no patterns of change with time or differences between the treatment groups observed.¹ There were no clinically significant changes from baseline for ESRS between treatment groups, and changes that occurred were small.¹ No post-baseline responses were noted on the C-SSRS, with no suicidal behavior or attempts in any subjects.¹

In the Meltzer et al study, a clinically meaningful change from baseline to day 85 in PANSS total score was demonstrated for the aripiprazole lauroxil 441 mg and 882 mg groups, with placebo-adjusted least squares mean differences of -10.9 (1.8) ($P < .001$) and -11.9 (1.8) ($P < .001$).² These improvements for both of the treatment groups were observed as early as day 8. Both the 441 mg and 882 mg groups had significantly better CGI-I scores at day 85 compared to placebo ($P < .001$).² A Wilcoxon rank sum test was used to determine this. The number of patients who were much or very much improved was also significantly greater in both the 441 mg and 882 mg groups compared to placebo at every assessment after day 8. ($P < .05$ to $P < .001$).² The study also looked at adverse events in a similar fashion to the Turncliff et al study. The adverse events that occurred were mostly mild or moderate in intensity. The only serious

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adverse event that was considered related to the study drug was akathisia in a patient in the 882 mg group.² More patients in the placebo group discontinued the study due to adverse events (17.9%) compared to the 441 mg group (6.8%) or the 882 mg group (2.9%), attributed to exacerbation of the underlying illness.² Treatment-emergent adverse events occurred in $\geq 2\%$ of patients in the treatment groups. The most common of these were insomnia, akathisia, headache, and anxiety.² Akathisia was the only treatment-emergent adverse event that occurred with an incidence $\geq 5\%$ in each treatment group that was double the incidence in the placebo group.² Most ($>75\%$) of the episodes of akathisia occurred before the second injection of aripiprazole lauroxil was administered. The incidence of injection site reactions was low overall, with 8 (3.9%), 12 (5.8%) and 4 (1.9%) patients for the 441 mg, 882 mg and placebo groups respectively.² The most common injection site reaction was pain, with redness, swelling or induration rarely reported.² Data on p-values from the trial is included in Table 2.

Table 2

	441 mg Aripiprazole Lauroxil	882 mg Aripiprazole Lauroxil
Placebo-adjusted least square mean difference improvement in PANSS baseline to day 85	-10.9 (1.8)	-11.9 (1.8)
P value	P<.001	P<.001
Placebo-adjusted mean change in PANSS day 85	-14.7 (3.5)	-16.6 (3.4)
P value	P<.0001	P<.0001

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Finally, in the Citrome et al study, the mean baseline PANSS total scores showed that patients in the study were severely impaired (score >90).³ The mean total PSP score at baseline was ≈ 50 , indicating severe difficulties with social and personal functioning.³ The proportion of patients with a PANSS hostility item P7 more than 1 was significantly lower for each aripiprazole lauroxil group compared to placebo at the end of the study.³ At day 85, aripiprazole lauroxil 441 mg 53.6% (P=0.01), aripiprazole lauroxil 882 mg 46.1% (P<0.001) and placebo 66.3%.³ Statistically significant changes were also observed at days 22, 29, and 57 of the study.³ When measuring the PANSS excited component, a significant improvement (P<0.001) was observed with both aripiprazole lauroxil groups compared with placebo at days 8, 15, 22, 29, 57, and 85.³ The improvement was greater in the 882 mg group compared to the 441 mg group. Significant improvements were observed for both aripiprazole lauroxil groups versus placebo for the PSP disturbing and aggressive behavior domain at day 85. These results were placebo 44.1%, aripiprazole lauroxil 441 mg 30% (P=0.007 vs. placebo) and aripiprazole lauroxil 882 mg 22.2% (P<0.001 vs. placebo).

DISCUSSION

The three studies combined display evidence that Aristada can be used as both a safe and effective treatment of schizophrenia. The Turncliff et al study demonstrated that IM administration of aripiprazole lauroxil is tolerable in adult patients with chronic stable schizophrenia.¹ The higher incidence of injection site reactions in the deltoid administration group shows that gluteal injections may be the preferred method in the future for patients who have a lower tolerance for pain. The most common injection site reaction being pain is not surprising as some small level of pain can be expected with IM injections. Still, only 43.5% of

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subjects experienced this adverse event.¹ Patients who experience dyskinesia or dystonia may be better served receiving their injection via gluteal administration as well since no subjects in the gluteal group experienced those adverse events.¹ The lack of clinically significant changes to vital signs, physical examination, and ECG demonstrate that while some mild adverse events may occur, overall it is safe to administer aripiprazole lauroxil IM. A limitation to this study was the smaller amount of patients who participated in it.

The Meltzer et al study showed that clinically and statistically significant negative changes occurred to the PANSS scores, meaning that both treatment groups were effective at reducing the symptoms of schizophrenia.² The drug may begin to work as early as 8 days after administration as evidenced by the study.² The statistically significant, improved CGI-I scores at day 85 of the study also supports that Aristada can effectively treat schizophrenia.² The greater improvement in the PANSS total score in the 882 mg group suggests that it may be more beneficial to administer a higher dose in patients with more severe symptoms.² This randomized, double-blind, placebo controlled trial also showed that Aristada is a safe option for schizophrenic patients. Both doses were well tolerated among patients with the incidence of treatment emergent adverse events remaining low and not appearing to be related to dose. Akathisia occurred in patients in both groups and seemed to coincide with the first injection for the majority of episodes. This is something that a follow-up study could more closely examine to further investigate the incidence of adverse events of aripiprazole lauroxil.

The Citrome et al study showed similar results to the two previously mentioned trials. The patients were found to have severe social and personal functioning based on PANSS scores at baseline, and these improved dramatically after the administration of aripiprazole lauroxil.³

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The PANSS hostility item P7 improvements seen in patients, demonstrate that reductions in hostile behaviors occurred.³ The reductions in aggressiveness and hostility are important to note because these are symptoms commonly seen in schizophrenic patients. This study provides more evidence that aripiprazole lauroxil can effectively reduce symptoms of schizophrenia in chronic schizophrenics who are severely affected by the disorder.

CONCLUSION

Based on this systematic review and its included studies, Aristada (aripiprazole lauroxil) is an effective and safe treatment for schizophrenia in adult patients. All three studies showed that the drug was well tolerated and was able to reduce symptoms of schizophrenia. The risks of the mild to moderate adverse events experienced by patients in the trials do not outweigh the benefits of effectively reducing symptoms associated with schizophrenia including agitation and hostility. Patients who wish to exhibit better control of their schizophrenic symptoms may find Aristada to be their treatment method of choice. Aristada may still be combined with other forms of treatment such as psychosocial support and cognitive behavioral therapy to achieve the greatest individualized results for patients. Future studies on Aristada could focus on more long-term effectiveness of Aristada over the course of a year. Future studies could also focus on how effective Aristada is when combined with other treatments for schizophrenia such as cognitive behavioral therapy. There is still more research to be done about Aristada but the results of the studies included in this evaluation demonstrate that it is a drug worth keeping on the radar of Physician Assistants and other healthcare practitioners across the country. It is with the knowledge of treatment options like Aristada that Schizophrenia can be effectively treated for symptomatic control and to reduce healthcare costs.

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