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Does the Addition of Piracetam Safely and Effectively Improve Behavioral and or Cognitive Functions in Schizophrenia?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective evidence based medicine (EBM) review is to determine whether or not the addition of piracetam safely and effectively improve behavioral and or cognitive functions in schizophrenia.

STUDY DESIGN: The selected review from all English language, primary literature sources that were published between 1979 and 1999.

DATA SOURCES: Three double blind randomized controlled trials (RCT) and one case controlled clinical study that compared piracetam to a visually matched placebo was selected and found using Medline, PubMed, Ebscohost, and Cochrane databases.

OUTCOMES MEASURED: Each of the trials assessed the effect of Piracetam on behavioral and or clinical functions of Schizophrenia patients by utilizing the following assessment tools: Brief Psychiatric Rating Scale (BPRS), The Behavior Rating Scale, The Wing Symptom Rating, and Positive and Negative Syndrome Scale (PANSS).

RESULTS: The trials demonstrated that the mean change before treatment with the use of piracetam as opposed to the visually matched placebo, as compared to after the treatment was large, with all statistically significant P values ≤ 0.05. This demonstrated that there was improvement in behavioral and cognitive functions achieved with the treatment of piracetam versus placebo.

CONCLUSION: Based on the studies, all reported that with the use of piracetam in schizophrenia, there showed improvement of some type of behavioral and or cognitive functions above baseline. Although the pattern of outcome was similar in all the studies, there requires a continued and more updated investigation to be aimed at determining a specific dose of piracetam therapy, a specific patient population for which piracetam is most effective and to further elaborate its safety profile outside a controlled research setting.

KEY WORDS: Piracetam, Nootropic Drugs, Psychosis, Psychiatric, Schizophrenia, Behavioral Functions, Cognitive Functions

INTRODUCTION

Schizophrenia is a pervasive, debilitating mental disease characterized by positive symptoms of hallucinations, delusions, and thought disorder (also referred to as psychosis), and negative symptoms of chronic social dilapidation.[1] The exact mechanism of schizophrenia is unknown although research continues to suggest that both chemical and physical abnormalities such as excess amounts of neurotransmitter dopamine or unusual chemical balance are associated with schizophrenia. There are also identifiable risk factors such as increasing parental age, winter birth, early development insults, migration, and genetic linkages.[2] It is observed in ~6.6% of all first-degree relatives and if both parents are affected, the risk of offspring is 40%.[3]

On average the incidence of people suffering from schizophrenia annually is 35 per 100,000 in population and there is a 1% prevalence in the world that a person will manifest the condition during their lifetime, thus making it more common than diabetes, Alzheimer's disease, and multiple sclerosis.[3] It typically begins in adulthood with the average onset for men between 18-25 years old and women between 25-35 years old.[4] Schizophrenic patients makes up almost 30% of new admissions to psychiatric institutions and occupy about half the beds in mental hospitals.[2] There is not an exact number of healthcare admissions each year due to the broad category of mental illness, however, there is an estimated 300,000 episodes of acute schizophrenia occurring annually in the United States with costs estimating to be over 50 billion dollars.[5] Therefore, it is crucial that the Physician Assistants or other healthcare providers be able to identify the condition and initiate treatment for the patients.

Schizophrenia appears to be a heterogeneous collection of many distinct diseases, which remain poorly defined but linked by common clinical features. Three major symptom clusters are seen in schizophrenia: positive, negative, and cognitive symptoms. Positive symptoms include hallucinations and delusions, experiences that are not characteristic of normal mental life. Negative symptoms represent deficits in normal functions such as blunted affect, impoverished speech, asocial behavior, and diminished motivation. Cognitive symptoms include deficits in working memory and cognitive control of behavior that often prove extremely disabling.[6] Some additional examples of cognitive control of behavior are organizing, problem solving or task switching. Schizophrenia remains a clinical diagnosis made on the basis of the individual's psychiatric history and mental status examination, as no laboratory or imaging studies can validly diagnose it.[7] Physician Assistants in primary care may be one of the first providers to encounter schizophrenia patients, so having knowledge and a high clinical suspicion may help establish a diagnosis and treatment plan more rapidly.

The general treatments for schizophrenia are atypical antipsychotics used to block receptors in the brain's dopamine pathways. They are the cornerstone in acute and maintenance treatment of schizophrenia. Atypical antipyschotics also known as second generation antipyschotics include aripiprazole, olanazapine, quetiapine, risperidone, and ziprasidone.[8] The atypical antipsychotic treatment options for schizophrenia all play an effective role on patients with schizophrenia. However, as with all medications, each option will have a different effect on each patient. Current general atypical antipsychotic drugs are efficacious for negative symptoms and cognitive only and generally lack efficacy for positive symptoms.[6] For positive symptoms, typical antipsychotics such as haloperidol, chlorpromazine, and fluphenazine can be used. However, these drugs have two major drawbacks: it is often difficult to find the best dosage level

for the individual patient, and a dosage level high enough to control psychotic symptoms frequently produces extrapyramidal side effects, or EPS.[4] Successful treatment of the disorder, therefore, requires attention not only to psychopathological domains such as positive and negative symptoms, but also to cognition and functional capacity. Cognitive dysfunction is an important treatment goal of piracetam. Piracetam is a nootropic drug that improves one or more aspects of mental functions, predominantly cognitive functions such as working memory, motivation and attention.[8] Piracetam may be used as an oral supplement for the relief of negative symptoms of schizophrenia and in improving cognitive functions will also improve behavioral functions. Although treatment with piracetam, used off label, has been shown to improve cognitive performance in schizophrenia and in other neuropsychological disorders worldwide, there is still lack of published reports evaluating the effects of the addition of piracetam on behavioral and cognitive functions in schizophrenia patients in the United States.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not the addition of piracetam is safe and effective in improving behavioral and or cognitive functions in adults with schizophrenia.

METHODS

To examine the objective question, this research paper focuses on adults (age $\geq$ 18 years old) with a diagnosis of schizophrenia or psychosis. All studies that were considered in the literature search included interventions of piracetam and a visually matched placebo, provided that the study had at least one arm including piracetam as an intervention and one without, to assess behavioral or cognitive functions. Types of studies considered were randomized control

trials; however, one study that was selected was a case controlled clinical study which includes data analysis. All patients in the selected articles had similar demographics and characteristics (Table 1).

Articles that were searched were peer reviewed journal published in the English language. A detailed search was performed through various search engines that included: Medline, PubMed, Ebscohost and Cochrane databases. Key words used in the search included: piracetam, nootropic drugs, schizophrenia, psychosis, psychiatric, behavioral functions, and cognitive functions. Articles were selected based on their relevance and importance of the outcome to the patient (Patient Oriented Evidence That Matters, POEMS). Inclusion criteria for the data sources consisted of double-blinded, placebo controlled RCTs that were the latest publishing available. Exclusion criteria consists of articles that included medications other than piracetam, did not compare with a placebo medical conditions aside from psychosis or schizophrenia, patients under age 18, pregnant, those with a concomitant physical disability, or having a language barrier. Statistics were then reported based on p-values, mean change from baseline, ANOVA F-score, relative benefit increase (RBI), absolute benefit increase (ABI), number needed to treat (NNT), and the following assessment scores: Brief Psychiatric Rating Scale (BPRS), The Behavior Rating Scale, The Wing Symptom Rating, and the Positive and Negative Syndrome Scale (PANSS), were used to assess the severity of the psychosis symptoms and rates them to guide the practitioner's route of therapy.

Table 1 - Demographics & Characteristics of included studies							
Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Chouinard G., Annable L., Ross-Chouinard A., Fontaine F. 1983[10]	RCT	60	54-80	diagnosed as having schizophrenia disorder/affective schizophrenic disorder; must satisfy psychiatric, neurologic and medical criteria	Pts with major cerebral impairment or focal cerebral lesion/ Pts with a major physical illness	1	Piracetam 800 mg 2 tablets TID
Dimond S., Scammell R., Pryce I., Huws D., Gray C. 1979[11]	RCT	24	38-63	male and female suffering from chronic schizophrenia; all patients were inpatient or residing in residential hostel	Concomitant physical illness, language difficulties, current disturbed behavior, or outside employment	0	Piracetam 800 mg 2 tabs TID
Noorbala A., Akhondzadeh S., Davari-Ashtiani R., Amini-Nooshabadi H. 1999[12]	RCT	34	18-41	Minimum score of 60 on the Positive and Negative Syndrome Scale (PANSS)	Significant organic, neurological disorders or serious psychotic disorders other than schizophrenia; pregnant or lactating women and those of reproductive age without adequate contraception	0	Piracetam 3200 mg/d
Kabes J., Erban L., Hanzlicek L., Skondia V. 1979[13]	Control Clinical Trial	14	23-50	Patients suffering from a functional psychosis	None stated	0	Piracetam 2400mg q/d

OUTCOMES MEASURED

The outcomes measured were based off each of the trials assessing the safety and efficacy of piracetam on several aspects of behavioral and cognitive functions. This included the mean change from baseline, dichotomous data, ANOVA, and PANSS. In the Chouinard and Kabes' study, efficacy was assessed with the Brief Psychiatric Rating Scale at mean change from baseline and conclusion that was also convertible into dichotomous data. Similarly, in the Noorbala study, efficacy was assessed via the PANSS at baseline and at conclusion looking at positive symptoms, negative symptoms and cognitive symptoms which was also further converted into analysis of variance with P-value. The Dimond study assessed efficacy utilizing the Wing Symptom Rating and the Behavior Rating Scale at baseline and at conclusion, in which data was converted into analysis of variance with F-score.

RESULTS

In order to review the studies, the 12^{th} week was chosen as the point of comparison for the Chouinard and Dimond studies while the closest measured time period was the 8^{th} week for the Noorbala and Kabes studies. The Chouinard et al study was a double blind RCT that consisted of 60 elderly patients ranging from 54-80 years old, although only 20 patients were randomly assigned to 12 weeks of treatment with piracetam and the others to placebo. Chouinard- specifically shows that with treatment, patients showed improvement in alertness and reported no withdrawal after discontinued use of the intervention and returned to their original condition within a month. The Dimond et al study was also a double blind crossover RCT that consisted of 24 patients ranging from 38-63 years old that participated in the study and was diagnosed with chronic schizophrenia. Dimond studied piracetam and the general facilitation of

performances producing fewer errors on this task which involves registering the tactual experience of number and preserving it in memory for recall. The Noorbala et al study, another double blind RCT was performed on 34 patients ranging from 18-41 years old and a minimum score of 30 on the PANSS was required for entry into the study. Noorbala studied piracetam with haloperidol and placebo with haloperidol and showed significant mean change from baseline with regards to PANSS. Finally, the Kabes et al study was a controlled clinical study with 14 participants, of which 11 were diagnosed with schizophrenia and 3 had some atypical depression symptoms. Kabes study shows there is a positive correlation b/w post treatment clinical improvement and biochemical levels using piracetam.

The mean change from baseline for improvement in behavior or cognitive functions, illustrated in Table 2, shows 1.2 for 800mg piracetam TID versus 0.3 for placebo, 29.148 for 800mg (2) piracetam TID versus 5.742 placebo, 2.610 for 3200mg piracetam versus 0.482 for placebo and finally 0.729 for 2400mg piracetam versus 0.175 for placebo. All studies show statistically significant p-values (Table 2) demonstrating efficacy with use of piracetam versus placebo.

Table 2- Efficacy based on mean change in behavior and cognitive functions

Study	Comparison	Mean Change from Baseline	P-value
Chouinard (1983)[10]	800mg piracetam TID	1.2	<0.001
	Placebo	0.3	
Dimond (1979)[12]	800mg (2) piracetam TID	29.148	0.01
	Placebo	5.742	
Noorbala (1999)[11]	3200mg piracetam	2.610	0.01
	Placebo	0.482	
Kabes (1979)[13]	2400mg piracetam	0.729	<0.01
	Placebo	0.175	

For analysis purposes, continuous data was converted into dichotomous data in the Chouinard and Kabes study. Based on the BPRS assessment, the Chouinard study reported 1.2 of patients on 800mg piracetam TID saw improvement in behavior or cognition function as compared to 0.3 on placebo, yielding a significant p-value <0.001(Table 3). The corresponding NNT was 1, meaning that for every 1 patient treated with 800mg piracetam TID, 1 will see improvement as compared to placebo. The Kabes study reported that 0.79 of patients on 800mg (2) piracetam TID saw improvement versus 0.21 on placebo, yielding a p-value <0.01 with a NNT of 2, so for every 2 patients treated with 800mg (2) TID piracetam, 1 will see improvement as compared to placebo.

Table 3- Efficacy based on Brief Psychiatric Rating Scale

Study	Comparison	Improvement from baseline	RBI	ABI	NNT	P-value
Chouinard[10]	800mg piracetam TID	1.2	3.0	0.9	1	<0.001
	Placebo	0.3				
Kabes[13]	2400mg piracetam	0.79	1.93	0.52	2	<0.01
	Placebo	0.21				

Finally, the Dimond study measured efficacy with the Wing Symptom Rating and the Behavior Rating Scale and used ANOVA to calculate F-score. (Table 4) Patients taking 800mg piracetam TID versus placebo yielded an F-score of 5.0718 and a p-value 0.01, statistically significant values, meaning improvement was shown in those taking piracetam versus placebo. In addition, in the Noorbala study, the PANSS was used to measure efficacy and repeated measures of ANOVA with a two-tailed post hoc tukey showed a significant effect of protocols on PANSS total scores with a significant p-value of <0.001.

Table 4- Efficacy based on ANOVA in behavior and cognitive functions

Study	Comparison	Mean	F-score	P-value
Dimond[12]	800mg piracetam TID	29.148	5.0718	0.01
	Placebo	5.742		

With regard to safety or adverse events, it was not addressed any of the studies reviewed.

DISCUSSION

Behavioral and cognitive dysfunction are just some of the very few symptoms experienced in schizophrenia, however if left untreated, it can be disabling to the patient. Although comparison of the studies, Table 2, showed statistically significant improvement in behavioral or cognitive functions with the treatment of piracetam versus a placebo, further clinical investigation is required to explain the discrepancy between the doses of piracetam in different individuals as well as what other specific psychotropic agents the patients were taking.

Analysis of the Brief Psychiatric Scale (Table 3) continues to support the efficacy of piracetam in that there is a significant improvement of behavioral and cognitive functions with p-values of < 0.001 and NNT of 1 and p-values of <0.01 and NNT of 2. This further demonstrates that with the addition of piracetam, it is more efficacious than the placebo. Finally, when evaluating efficacy in the Dimond study, ANOVA was used and calculated an F-score of 5.0718, meaning that of the groups that are different, variance is due to something other than chance. In this study, the F-score is also significant.

Due to the various discrepancies across all data (the specific dosages of the intervention and the timeframe/duration of the study and the patient population), it cannot be used to compare treatments across all studies equally. Therefore, analysis and further larger clinical trials

regarding optimal dosing is required. Limitations across studies included various discrepancies such as the different dosages of controlled drug, Piracetam; the various duration of timeframe of the studies; lack of producibility of whether or not taking the controlled drug was safe or if there was any side effects. Additional limitations include lack of current published studies, small sample sizes and discrepancies in the type of patient tested as well as differences in the number of patients studied, and numerous methods to evaluate the effects of piracetam on behavioral and cognitive functions in patients with schizophrenia. With all these limitations, there is a possibility that it may have affected the statistical power of the study to detect significant treatment differences.

At the present moment, it appears piracetam lacks a future in the United States for its uses as an adjuvant therapeutic option for schizophrenia because although piracetam has various off-label uses which makes it appealing to practitioners, the FDA has not approved its use in the United States.

CONCLUSION

Piracetam is a nootropic drug that can improve mental functions in patients with schizophrenia, however, based on the analysis of the four trials that were included in this review; it is inconclusive if the addition of piracetam will safely and effectively improve behavioral or cognitive functions in patients with schizophrenia. Although there are statistically significant outcomes, it is unclear whether the results are clinically significant enough to warrant changes to the management of this disease. Furthermore, future research is warranted since there is lack of current published studies, small sample sizes, insufficient data illustrating calculations, and

numerous methods to evaluate the effects of piracetam on behavioral and cognitive functions in patients with schizophrenia.

In some countries, piracetam is available over the counter and is used outside of a controlled setting whereas in the United States, it is not FDA approved and therefore not available. Future research should include whether or not patients have comorbid conditions, whether or not patients are relapsing, address the optimal dosing schedule for piracetam administration and if piracetam is used in conjunction with other psychotropics for it to be uniformed throughout, the season that the patients were treated in, and whether or not the patient's improvement is the same in a controlled or uncontrolled environment. Until such research is performed, determination of its true safety profile cannot be validated.

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