

# Expert Perspectives on the Prescription Practice of Citicoline and Piracetam, Both as Monotherapy and in Combination for Stroke Management in Indian Settings

## Research Article

Manjula S\* and Krishna Kumar M

*Department of Medical Services, Micro Labs Limited, Bangalore, Karnataka, India*

\*Corresponding author: Manjula S, Department of Medical Services, Micro Labs Limited, Race Course Road, Bangalore, Karnataka, India. Email Id: [drmanjulas@gmail.com](mailto:drmanjulas@gmail.com)

**Article Information:** Submission: 12/11/2024; Accepted: 06/12/2024; Published: 09/12/2024

**Copyright:** © 2024 Manjula S, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

### Abstract

**Background:** Although there are several studies available regarding the efficacy and safety of citicoline and piracetam for stroke management, studies among clinicians in actual practice are scarce. This study aims to gather expert perspectives on the clinical use and prescribing practice of citicoline and piracetam, both as monotherapy and combination therapy, for stroke management in Indian clinical settings.

**Methodology:** This cross-sectional study was conducted with a 24-item questionnaire among clinicians specializing in stroke management. The survey assessed prescription practices, clinical observations, and preferences regarding citicoline and piracetam, both as monotherapy and combination therapy, as well as overall stroke management. Data analysis employed descriptive statistics, with results reported as frequencies and percentages.

**Results:** The survey included 439 experts and nearly 55% of participants identified elderly patients as the most affected by acute ischemic stroke (AIS). Around 43% noted that the increased use of intravenous thrombolysis (IVT) has revolutionized AIS treatment. Nearly 63% of the clinicians observed the occurrence of cognitive decline in stroke patients. Most clinicians (71.75%) preferred a combination of piracetam and citicoline as neuroprotective agents, with 51% emphasizing the benefits of citicoline in restoring mitochondrial ATPase and Na<sup>+</sup>/K<sup>+</sup> ATPase activity. About 37% of clinicians highlighted better tolerability with fixed combinations. Most (94.99%) recommended 800 mg piracetam and 500 mg citicoline, with tablets being the preferred dosage form for 91.8% of the participants.

**Conclusion:** The survey reveals clinicians' preference for combining piracetam and citicoline as neuroprotective agents in stroke management, particularly for role of citicoline in restoring mitochondrial ATPase activity. However, challenges with patient adherence and education hinder treatment optimization. Further research is needed to evaluate the efficacy, tolerability, and long-term benefits of this therapy

**Keywords:** Stroke; Piracetam; Citicoline; Neuroprotective; Hypertension

## Introduction

Stroke is recognized as one of the most devastating neurological conditions worldwide, responsible for approximately 5.5 million deaths annually and contributing to a loss of around 44 million disability-adjusted life-years. With the increasing prevalence of the aging global population, stroke has become the second leading cause of death globally, highlighting the urgent need for effective prevention and treatment strategies [1,2]. In India, the impact of stroke is particularly pronounced. A 2016 estimate from the Global Burden of Disease project reported 1,175,778 new stroke cases in the country. A recent systematic review, primarily based on cross-sectional studies, indicated that the incidence of stroke in India ranges from 105 to 152 cases per 100,000 people annually. This highlights a significant public health challenge that necessitates immediate attention and action [3,4]. In stroke treatment, citicoline, a nootropic, has emerged as a promising therapeutic agent, exerting effects at various stages of the ischemic cascade during acute ischemic stroke (AIS) [5]. Citicoline stabilizes cell membranes by promoting phosphatidylcholine and sphingomyelin synthesis and inhibiting the release of free fatty acids. By protecting these membranes, citicoline reduces glutamate release during ischemic events, providing neuroprotective benefits [6]. Another drug of interest is piracetam, also classified as a nootropic. It enhances cognitive functions associated with learning and memory, particularly in healthy individuals. While its exact mechanisms remain somewhat unclear, piracetam may enhance cholinergic neurotransmission, suggesting potential benefits for cognitive recovery post-stroke [7]. The combination of citicoline and piracetam offers enhanced neuroprotective effects and demonstrates improved quality of life [8].

The current survey aims to gather expert opinions on stroke management and the prescribing practices for citicoline and piracetam, both as monotherapies and in combination, within Indian healthcare settings. This effort is crucial for addressing the increasing burden of stroke in the country, optimizing stroke care, and improving patient outcomes.

## Methods

We carried out a cross-sectional study among clinicians specialized in treating stroke patients in the major Indian cities from June 2023 to December 2023.

## Questionnaire

The questionnaire booklet titled NICE (Citicoline and Piracetam in Stroke – Expert perspective study) was sent to the physicians who were interested to participate. The study questionnaire included 24 questions focused on current prescription practices, clinical observations, and preferences related to citicoline and piracetam, both as combination and monotherapy, as well as clinicians' experiences with stroke in routine practice. The study was conducted after receiving approval from Bangalore Ethics, an Independent Ethics Committee which is recognized by the Indian Regulatory Authority, Drug Controller General of India. Survey questions were developed using the methods designed to collect perspectives from the practitioners. Reliability as determined by a split-half test (coefficient

alpha) was adequate but should be improved in future versions of the questionnaire. A study of criterion validity was undertaken to test the questionnaire and to develop methods of testing the validity of measures of Physicians Perspectives. However, the extraneous variable in this includes the clinicians experience, usage of the newer drugs etc. The two criteria used were the doctors' perspectives from the clinical practice and the assessment of an external assessor and statistician.

## Participants

Convenience sampling method was adopted where an invitation was sent to leading clinicians who were expertise in managing stroke in the month of March 2023 for participation in this Indian survey. About 439 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. Those physicians were included and asked to complete the questionnaire without discussing with peers. A written informed consent was obtained from each neurologist's prior initiation of the study. Clinicians who were expertise in other specialities and were not provided informed consent were excluded from the study.

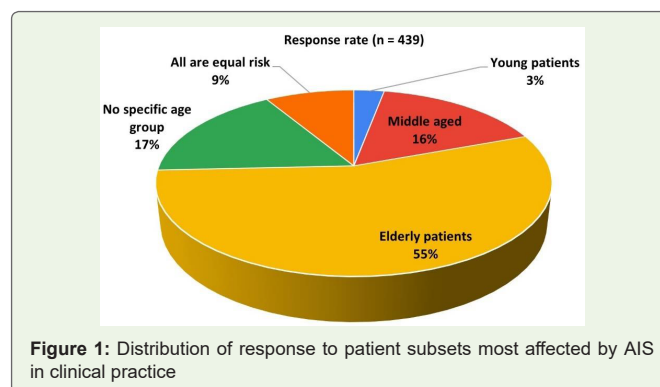
## Statistical analysis

The data were analyzed using descriptive statistics. Categorical variables were presented as percentages to depict their distribution. The frequency of occurrence and the corresponding percentage were used to represent the distribution of each variable. To visualize the distribution of the categorical variables, pie, and bar charts were created using Microsoft Excel 2013 (version 16.0.13901.20400).

## Results

The survey included 439 neurologists, with 26% reporting that 6-15% of stroke patients arrive within the golden hour in clinical settings. Around 45% indicated that 11-20% of patients and caregivers are aware of the golden hour for stroke. Approximately 42% reported that 26-50% of stroke patients had a history of COVID-19 within the past two years. Nearly 55% identified elderly patients as the group most affected by AIS in clinical practice [Figure 1].

Approximately 29% of respondents indicated that 16-25% of patients presenting to clinical settings have AIS, while around 28% reported that 6-15% experience hemorrhagic stroke. About 55% noted that 26-50% of stroke patients have comorbid hypertension.



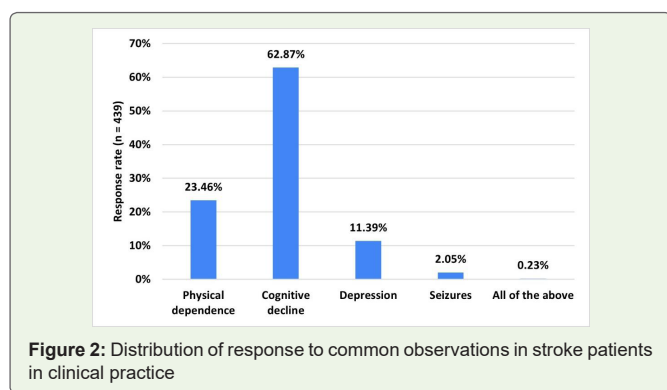
Additionally, 43% of clinicians highlighted that the increased use of intravenous thrombolysis (IVT) has revolutionized AIS treatment over the past two decades [Table 1].

About 33% of participants reported excellent results for all patients treated during golden hour. Approximately 52% identified patient adherence to regular medication as one of the most challenging aspects of stroke management in clinical practice. Nearly 41% highlighted lack of patient education as a contributing factor to non-adherence to medication. Additionally, about 63% of clinicians observed cognitive decline as a common occurrence in stroke patients [Figure 2].

Around 44% of the experts reported that mass education, particularly through social media, was the preferred method for educating stroke patients. More than half (51.71%) of the participants reported that neuroprotective agents in stroke management offer benefits in improving functional outcomes and quality of life. About 36% of participants indicated that 25-50% of patients were prescribed neuroprotective agents in clinical practice. The majority (71.75%) of the participants preferred a combination of piracetam and citicoline as neuroprotective agents for stroke management [Table 2]. More than half (51.03%) of the respondents emphasized the benefits of citicoline in stroke patients, particularly its role in restoring mitochondrial ATPase activity and membrane Na<sup>+</sup>/K<sup>+</sup> ATPase [Table 3].

**Table 1:** Distribution of response to the revolution in the treatment of AIS over the last two decades

Revolution in the treatment of AIS	Response rate (n = 439)
Increasing use of intravenous thrombolysis	43.05%
Advent of endovascular therapy (EVT)	20.27%
Newer advances in pharmacotherapy	18.68%
Increased awareness and appropriate care	17.77%
All of the above	0.23%



**Figure 2:** Distribution of response to common observations in stroke patients in clinical practice

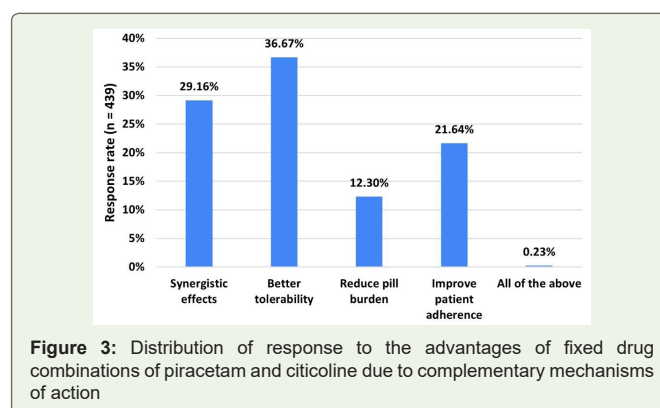
**Table 2:** Distribution of response to preferred neuroprotective agents in stroke management

Preference	Response rate (n = 439)
Piracetam	23.92%
Edaravone	2.51%
Cerebrolysin	1.82%
Combination of piracetam and citicoline	71.75%

Around 52% of participants reported that 26-50% of patients were prescribed a combination of piracetam and citicoline. About 37% highlighted the advantages of fixed drug combinations of piracetam and citicoline, noting improved tolerability due to their complementary mechanisms of action [Figure 3]. Most clinicians (94.99%) recommended 800 mg of piracetam and 500 mg of citicoline as the commonly prescribed strengths for AIS treatment [Table 4]. Approximately 55% of participants reported that the recommended duration for combination therapy with piracetam and citicoline in stroke patients was 1-3 months. The majority (91.8%) of the participants indicated that tablets were the preferred dosage form for the piracetam and citicoline combination in stroke management [Figure 4].

**Table 3:** Distribution of response to the benefits of citicoline in stroke patients

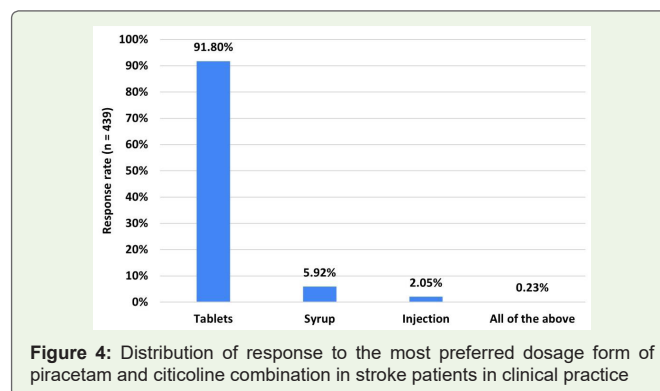
Benefits	Response rate (n = 439)
Restoring the activity of mitochondrial ATPase and membrane Na <sup>+</sup> /K <sup>+</sup> ATPase	51.03%
Inhibits the activation of phospholipase A2	22.55%
Accelerates the reabsorption of cerebral edema	26.2%
Not attempted	0.23%



**Figure 3:** Distribution of response to the advantages of fixed drug combinations of piracetam and citicoline due to complementary mechanisms of action

**Table 4:** Distribution of response to commonly prescribed strengths of piracetam and citicoline for AIS treatment

Strengths of piracetam and citicoline	Response rate (n = 439)
Piracetam 800 mg + Citicoline 500 mg	94.99%
Piracetam 400 mg + Citicoline 500 mg	5.01%



**Figure 4:** Distribution of response to the most preferred dosage form of piracetam and citicoline combination in stroke patients in clinical practice

Nearly half (48.52%) of experts opined that the combination of piracetam and citicoline was beneficial for improving cognitive decline during post-stroke recovery. About 51% of clinicians indicated that patients with neurological and cognitive disorders are the most prescribed subset for this combination in clinical practice.

## Discussion

The current study has highlighted the combination of piracetam and citicoline as the preferred neuroprotective strategy, particularly for enhancing cognitive recovery in post-stroke patients. The survey also underscored the significance of improved patient education on the golden hour and medication adherence for optimizing stroke outcomes.

More than half of the current respondents identified elderly patients as the most affected group by AIS in clinical practice. In concurrence with this finding, Fonarow et al. noted that age is the most significant unmodifiable risk factor for all types of strokes, including ischemic stroke. They found that for every 10-year increase in age after 55, the stroke rate more than doubles in both the genders [9]. Pundik et al. highlighted that older adult experience a significantly higher incidence of ischemic stroke, along with increased mortality and morbidity rates compared to younger patients [10].

Many of the respondents noted that the increased use of IVT has revolutionized the treatment of AIS over the past two decades. Advani et al. highlighted that the treatment of AIS has undergone a revolution over the past two decades, driven by the growing use of IVT and the introduction of EVT [11]. Ungerer et al. noted that AIS treatment has undergone tremendous changes in the past decade, particularly with the establishment of dedicated stroke units and the recognition of IVT as an effective treatment [12].

Many of the participants reported cognitive decline as a common observation in stroke patients in clinical practice. Al-Qazzaz et al. found that cognitive impairment and memory loss are common occurrences following a stroke [13]. Lo et al. found that patients who have had a stroke experience a more rapid cognitive decline compared to stroke-free controls within the first 1 to 3 years after onset. They also observed that older age and recurrent strokes are associated with an increased rate of cognitive decline [14].

Majority of the respondents preferred a combination of piracetam and citicoline as neuroprotective agents for stroke management. Another study by the same authors concluded that piracetam and citicoline were the most commonly prescribed neuroprotective treatments, with AIS being the most frequently observed type, followed by cerebral hemorrhage [15]. Ricci et al. suggested that piracetam exhibits neuroprotective and antithrombotic properties, which could potentially reduce mortality and disability in individuals with AIS [16]. Clark et al. found that oral citicoline can be used safely with minimal side effects in the treatment of AIS [17]. More than half of the current survey participants emphasized the benefits of citicoline in stroke patients, particularly its role in restoring mitochondrial ATPase activity and membrane Na<sup>+</sup>/K<sup>+</sup> ATPase. Bermejo et al. demonstrated that citicoline helps restore the activity of mitochondrial ATPase as well as the membrane-bound Na<sup>+</sup>/K<sup>+</sup>

ATPase [18]. Hatcher and Dempsey found that citicoline plays a role in restoring the activity of Na<sup>+</sup>/K<sup>+</sup>-ATPase [19].

Many of the participants highlighted the benefits of fixed-dose combinations of piracetam and citicoline, noting improved tolerability due to their complementary mechanisms of action. However, studies specifically investigating the enhanced tolerability of these combinations through their synergistic effects are lacking, indicating the need for further research. While there is substantial literature supporting the benefits of piracetam and citicoline in treating cognitive disorders, the potential advantages of piracetam, particularly when combined with citicoline, remain uncertain in stroke patients due to the lack of well-controlled studies. Álvarez-Sabín and Román concluded that citicoline was both safe and effective, aiding in the improvement of cognitive decline following a stroke and supporting better functional recovery in patients [20].

Most of the respondents stated 800 mg of piracetam and 500 mg of citicoline as the commonly prescribed strengths for AIS treatment. Doijad et al. reported that a fixed-dose combination of citicoline (500 mg) and piracetam (800 mg) was commonly prescribed for memory enhancement, neurological and cognitive disorders, Parkinsonism, and Alzheimer's disease. These drugs function as cognition-enhancing supplements and are recommended in treatment regimens at certain aging clinics. Additionally, taking citicoline with piracetam helps reduce the headache typically induced by piracetam [21]. Clark et al. suggested that citicoline may enhance functional outcomes and reduce neurological deficits, with 500 mg being the optimal dosage [17]. In another study by the same author, piracetam 800 mg is reported to be frequently prescribed to most stroke patients [15].

Majority of the respondents reported that tablets are the most preferred dosage form for the piracetam and citicoline combination in stroke patients in clinical practice. Doijad et al. and Ebrahimi et al. have reported the availability of the citicoline and piracetam fixed-dose combination in the form of film-coated tablets on the market for the treatment of various neurological conditions [21,22].

The strength of the survey lies in its large sample size and the use of a well-crafted multi-response questionnaire. The study identifies elderly patients as the most affected by AIS, consistent with existing research. The insights into clinician preferences for neuroprotective treatments, particularly the combination of piracetam and citicoline, may help optimize the treatment approach. However, the study has limitations, including potential survey bias, reliance on secondary literature rather than primary experimental data, and the absence of longitudinal data.

## Conclusion

The survey highlights a strong preference among clinicians for the combination of piracetam and citicoline as neuroprotective agents in stroke management. Majority of the respondents recognized the benefits of citicoline, particularly its role in restoring mitochondrial ATPase activity, which contributes to improved outcomes. However, significant challenges related to patient adherence and education hinder the optimization of treatment. While the study provides valuable insights into clinician preferences and practices,

it underscores the need for further research to assess the efficacy, tolerability, and long-term benefits of combined therapies in stroke patients.

**Acknowledgement:** We would like to thank all the clinicians who were participated in this study

## References

- Mukherjee D, Patil CG (2011) Epidemiology and the Global Burden of Stroke. *World Neuro surg.* 76: S85-S90.
- Katan M, Luft A (2018) Global Burden of Stroke. *Semin Neurol* 38(02): 208-211.
- Johnson C, Owens C (2019) Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 18: 439-458.
- Kamalakkannan S, Gudlavalleti ASV, Gudlavalleti VSM, Goenkas S, Kuper H (2017) Incidence prevalence of stroke in India: A systematic review. *Ind J Med Res.* 146: 175-185.
- Grieb P, Świątkiewicz M, Kamińska A, Junemann A, Rejdak R, et al. (2021) Citicoline: A candidate for adjunct treatment of multiple sclerosis. *Pharmaceutics* 14: 326.
- Álvarez-Sabín J, Román GC (2013) The Role of Citicoline in Neuroprotection and Neurorepair in Ischemic Stroke. *Brain Sciences* 3: 1395.
- Piracetam - an overview. ScienceDirect Topics. Available from: <https://www.sciencedirect.com/topics/neuroscience/piracetam>
- Shibu A, Meera S, Gopal AV (2023) A comparative study on the assessment of neuroprotective effect of citicoline vs citicoline with piracetam and health related quality of life in post stroke patients. *World J Pharm Res* 8: 704-750.
- Fonarow GC, Reeves MJ, Zhao X, Olson DWM, Smith EE, et al. (2010) Age-Related Differences in Characteristics, Performance Measures, Treatment Trends, and Outcomes in Patients with Ischemic Stroke. *Circulation.* 121: 879-891.
- Pundik S, McWilliams-Dunnigan L, Blackham KL, Kirchner HL, Sundararajan S, et al. (2008) Older Age Does Not Increase Risk of Hemorrhagic Complications after Intravenous and/or Intra-Arterial Thrombolysis for Acute Stroke. *J Stroke Cerebrovasc Dis* 17: 266-272.
- Advani R, Naess H, Kurz MW (2017) The golden hour of acute ischemic stroke. *Scand J Trauma Resusc Emerg Med* 25: 54.
- Ungerer MN, Bartig D, Richter D, Krogias C, Hacke W, et al. (2024) The evolution of acute stroke care in Germany from 2019 to 2021: analysis of nation-wide administrative datasets. *Neurol Res Pract* 6: 4.
- Al-Qazzaz NK, Ali SH, Ahmad SA, Islam S, Mohamad K (2014) Cognitive impairment and memory dysfunction after a stroke diagnosis: a post-stroke memory assessment. *Neuropsychiatr Dis Treat.* 10: 1677.
- Lo JW, Crawford JD, Desmond DW, Lim JS, Godefroy O, et al.; Stroke and Cognition (STROKOG) Collaboration (2022) Long-Term Cognitive Decline After Stroke: An Individual Participant Data Meta-Analysis. *Stroke* 53: 1318-1327.
- Manjula S, Krishna Kumar M (2024) Expert opinion on stroke management: An Indian observational study. *IP Indian J Neurosci* 10: 4-8.
- Ricci S, Celani MG, Cantisani TA, Righetti E (2012) Piracetam for acute ischaemic stroke. *The Cochrane Database of Systematic Reviews* 2012: CD000419.
- Clark WM, Warach SJ, Pettigrew LC, Gammans RE, Sabounjian LA (1997) A randomized dose-response trial of citicoline in acute ischemic stroke patients. *Citicoline Stroke Study Group. Neurology* 49: 671-678.
- Bermejo PE, Dorado R, Zea-Sevilla MA (2023) Role of Citicoline in Patients with Mild Cognitive Impairment. *Neurosci Insights.* 18: 26331055231152496.
- Adibhatla RM, Hatcher JF, Dempsey RJ (2002) Citicoline: Neuroprotective mechanisms in cerebral ischemia. *J Neurochem* 80: 333-343.
- Álvarez-Sabín J, Román GC (2013) The Role of Citicoline in Neuroprotection and Neurorepair in Ischemic Stroke. *Brain Sciences* 3: 1395.
- Dojjad RC, Pathan AB, Pawar NB, Baraskar SS, Maske VD, et al. (2012) Therapeutic Applications of Citicoline and Piracetam as Fixed Dose Combination. *Asian J Biomed Pharm Sci.* 2: 15-20.
- Ebrahimi S, Esfahani SA, Ebrahimi A (2022) Comparison of the Effects of Citicoline and Piracetam on Hypoxic-ischemic Brain Damage in Neonatal Rabbits. *Iranian J Child Neurol.* 16: 77.