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Research Paper

Medical Science

KEYWORDS : Clozapine, Treatment resistant schizophrenia

A Study on Efficacy of CLOZAPINE in Treatment Resistant Schizophrenia

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ABSTRACT

AIMS AND OBJECTIVES : To study the efficacy of CLOZAPINE in Treatment Resistant Schizophrenia.To evaluate the association of schizophrenia with socio demographic characteristics and adverse effects during the course of treatment with Clozapine.

MATERIAL & METHODOLOGY : A short term, cross sectional, prospective & non comparative study was conducted among inpatients from Department of Psychiatry in Alluri Sita Rama Raju Academy of Medical Sciences, Eluru for a duration of 8 weeks.

RESULTS : • The mean positive symptom score showed a gradual improvement from 17 to 7 by the end of 8weeks which was found to be statistically significant (t=18.698, p<0.01).

• The mean negative symptom score showed a gradual improvement from 24 to 10 by the end of 8 weeks which was found to be statistically significant (t=18.880, p<0.01).

• The mean general psychopathology score showed a gradual improvement from 23 to 9 by the end of 8 weeks which was found to be statistically significant (t=25.225, p<0.01).

Common mild adverse effects were encountered but none of the patients treated with Clozapine developed Extra pyramidal symptoms, Agranulocytosis , Seizures & Myocarditis

CONCLUSION : Our study concluded that Clozapine is beneficial, relatively well tolerated and the ideal drug for Treatment Resistant Schizophrenia.

However, attention should be paid to patients' adverse events and precautions against Agranulocytosis should be taken.

INTRODUCTION

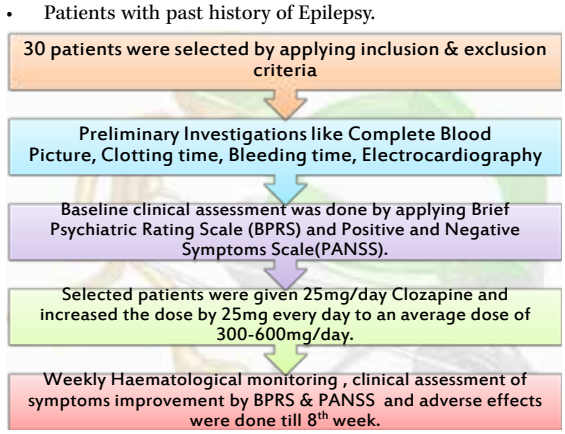
- Schizophrenia is a long term mental disorder, with profound disruptive psychopathology that involves cognition, emotion, perception, and behaviour.
- The mainstay of treatment has been antipsychotic medication but one third of people will have a 'treatment resistant' and the most disabling and costly illness.
- Treatment Resistant Schizophrenia is defined as an inadequate response to at least two antipsychotics belonging to two different classes at the maximally tolerated dose with in the recommended therapeutic range, in trials lasting six weeks or more.
- Termination of a medication due to adverse events before reaching the appropriate dose and duration should not be regarded as a failed trial due to non response to the medication.
- Clozapine was the first Atypical antipsychotic, introduced into market by Sandoz in 1960s and later withdrawn after reports of Agranulocytosis.
- In 2002, it was approved by FDA for Treatment Resistant Schizophrenia and Schizophrenia with suicidal risk.
- Mechanism of Action :
- It has multiple sites of action such as dopaminergic, serotonergic, cholinergic and histaminergic receptors, with high affinity to D4 and 5HT2A and low affinity to D1, D2 & D3 receptors which explains it's lower extra pyramidal symptoms liability & atypical profile.

AIMS AND OBJECTIVES

- To study the efficacy of CLOZAPINE in Treatment Resistant Schizophrenia.
- To evaluate the association of schizophrenia with socio demographic characteristics and adverse effects during the course of treatment with Clozapine.

MATERIAL & METHODOLOGY

- A short term, cross sectional, prospective & non comparative study was conducted among inpatients from Department of Psychiatry in Alluri Sita Rama Raju Academy of Medical Sciences, Eluru for a duration of 8 weeks.
- INCLUSION CRITERIA:
- Written consent from the spouse or close 1st degree relatives to participate in the study.
- Diagnosis of Schizophrenia made by two consultants independently, using ICD 10 criteria.
- Only Treatment Resistant Schizophrenia patients of various subtypes are included in this study.
- EXCLUSION CRITERIA:
- Patients with Total leukocyte count of less than 3,500 cells/ cubic mm.
- Patients of more than 45 years of age.
- Patients suffering from Bone marrow diseases like Leukaemia, Aplastic anaemia.
- Patients who are already on drugs that can cause Agranulocytosis or Bone marrow suppression like Carbamazepine, Sulpha drugs.
- Patients with Severe Arrhythmias, Bundle Branch blocks.
- Patients with past history of Epilepsy.



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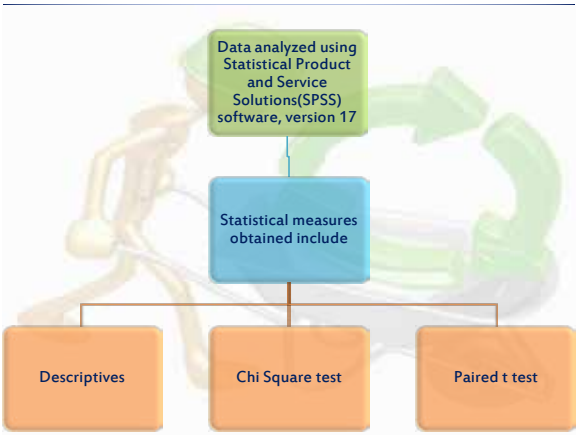
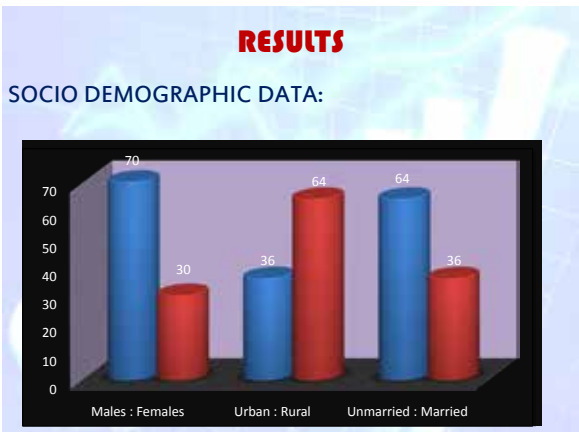
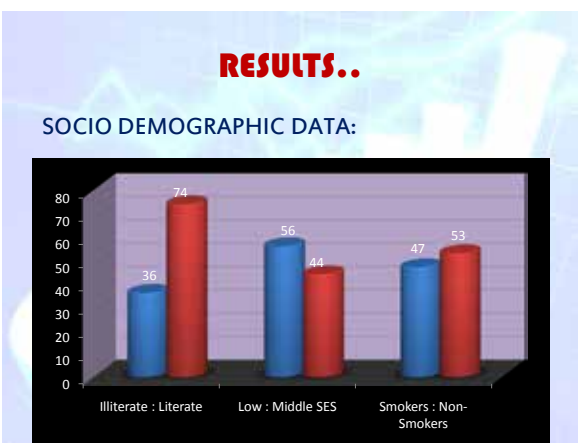
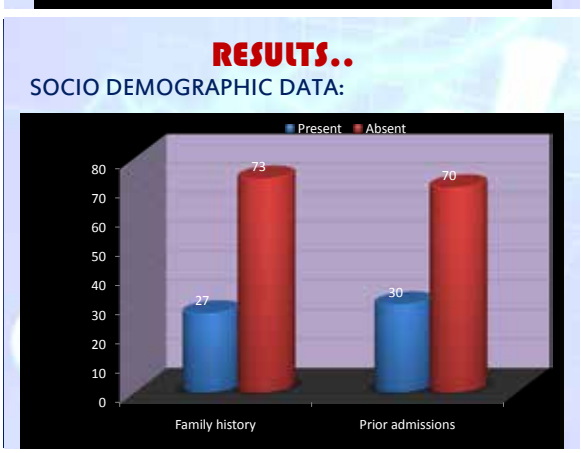
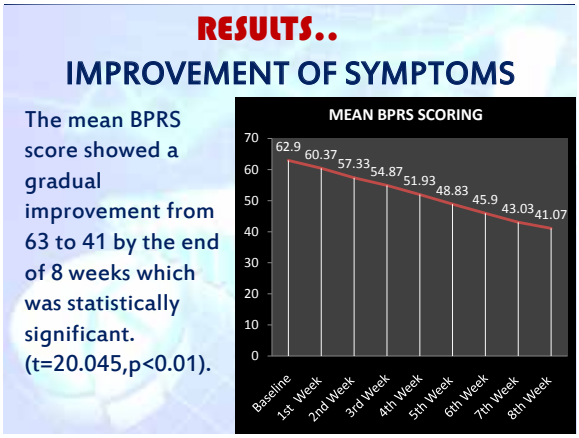


RESULTS









- The mean positive symptom score showed a gradual improvement from 17 to 7 by the end of 8weeks which was found to be statistically significant (t=18.698, p<0.01).
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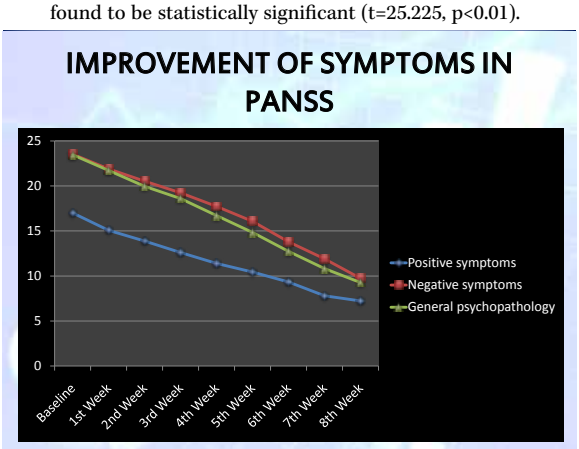
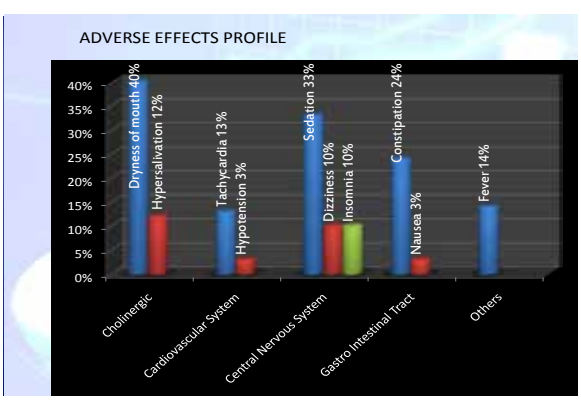


ADVERSE EFFECTS PROFILE

- Common mild adverse effects were encountered but none of the patients treated with Clozapine developed Extra pyramidal symptoms, Agranulocytosis , Seizures & Myocarditis.



DISCUSSION

- Approximately 20-25% of all patients with Schizophrenia are resistant to repeated attempts at treatment .
- For treating this population, Clozapine has been shown in several multicenter clinical trials to be gold standard.
- However, Black box warnings by FDA are Agranulocytosis,

Seizures & Myocarditis.

AUTHOR	STUDY	CONCLUSION
Kaneda Y et al(2010)	Study on Determinants of Work outcome in Neuroleptic-resistant schizophrenia & Schizoaffective disorder on Clozapine	Neurocognitive performance as indicated by Employment status increased to 48.9% over a 12 month period.
Kumra S et al (2008)	Comparative extended study on Clozapine vs Olanzapine in Refractory early onset Schizophrenia	70% of young patients with Schizophrenia who failed treatment with high dose(up to 30mg/day) were found to respond to a 12 week open label Clozapine trial.
Meltzer et al (2006)	Comparative study on the effectiveness of Clozapine to other atypical antipsychotics in Chronic Schizophrenia.	At 3 month assessment, PANSS scores had decreased more in patients with Clozapine than that of on Quetiapine, Risperidone & Olanzapine.
Kelly DL et al (2003)	Comparative study on Adverse effects and laboratory parameters of high dose Olanzapine Vs Clozapine in Treatment Resistant Schizophrenia.	Significant Response to Clozapine was found while none on Olanzapine responded to treatment. Anticholinergic effects were higher with Olanzapine .Increase in lipids and liver enzymes was found with Clozapine. Neither treatment was associated with Akathisia and Agranulocytosis
Alphs L et al (2004)	**The International Suicide Prevention Trial(InterSePT): Comparative study between Olanzapine Vs Clozapine in reducing suicidal behaviour.**	**Clozapine is more efficacious in reducing the suicidal behaviour in Schizophrenia and Schizoaffective patients.**
Meltzer et al (2012 Oct)	Clozapine-Balancing Safety with superior antipsychotic efficacy	The primary indications for clozapine are: 1) treatment-resistant schizophrenia or schizoaffective disorder2) patients with schizophrenia or schizoaffective disorder who are at high risk for suicide. Awareness of the benefits and risks of clozapine is essential.
Velligan DI etal (2014)	Outcomes of Medicaid Beneficiaries With Schizophrenia Receiving Clozapine Only or Antipsychotic Combinations	Among nonelderly adult Medicaid beneficiaries with schizophrenia, treatment with clozapine instead of antipsychotic polypharmacy was associated with reduced disease-specific emergency department use and with reduced disease-specific and all-cause health care costs.

- The risk of seizures is about 4% in patients taking doses >600mg/day.
- Clozapine induced Agranulocytosis has a prevalence of 0.73% during the 1st year of treatment.
- Though Agranulocytosis is a limiting factor for the liberal usage of Clozapine world wide, it was reported to be very rare.
- Careful and regular haematological monitoring would avoid the complications.

CONCLUSION

- Our study concluded that Clozapine is beneficial, relatively well tolerated and the ideal drug for Treatment Resistant Schizophrenia.
- However, attention should be paid to patients' adverse events and precautions against Agranulocytosis should be taken.

LIMITATIONS

- This is a cross sectional, randomised & non comparative study with a small sample size, conducted in one medical college.
- Further double blind, randomised controlled clinical trials should be conducted to further explore the utility of Clozapine in Treatment Resistant Schizophrenia.
- The socio demographic data may vary among different groups.
- So, this cannot be generalised to all the communities and societies.

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