LONG-TERM CLINICAL OUTCOMES OF CLOZAPINE USE IN ALLEGHENY COUNTY

Deepak K. Sarpal, M.D.
Assistant Professor
Department of Psychiatry
University of Pittsburgh

Medical Director
STEP Clinic
UPMC WPH

Outline

• Introduction/history of clozapine
• Current evidence/underutilization
• Study Rationale and Methods
• Study Results
• Conclusions and future directions
Introduction

• Up to 40% of patients with psychosis fail to respond to first-line antipsychotic drugs.

• Clozapine remains a unique antipsychotic drug for these patients:
  • consistently shows superior efficacy in patients who are refractory to treatment with other antipsychotic drugs.
  • Has anti-suicidal properties
  • Unique profile of action at receptors

• We don’t know the mechanism of action that makes clozapine unique. Patients who enter treatment with clozapine may represent a unique subset of patients.

• It is underutilized!

Burden of Treatment-Refractory Illness

Kennedy et al., 2014
Clozapine History: Timeline of Events

1954
Chlorpromazine
FDA Approved

1956
Clozapine
discovered

1975
Finnish
“Epidemic”

1975
Clozapine
discovered

1988
Kane et al.
Published

1989
Clozapine
FDA Approved

2003
InterSePT trial published

2015
REMS Established

Clozapine Efficacy

Siskind et al., 2016
Clozapine Efficacy

Figure 1. Cumulative Probability of a Significant Suicide Attempt or Hospitalization to Prevent Suicide in Patients with Schizophrenia or Schizoaffective Disorder at High Risk of Suicidality

- Neutropenia/Agranulocytosis
- Risk Evaluation and Mitigation Strategy (REMS) Program
  - “no blood, no drug”

Other important side effects: cardiac effects (myocarditis), constipation and bowel obstruction, weight gain, hypersalivation, tachycardia, seizures (higher doses & dose related)
Antipsychotic Treatment Algorithm

Underutilization

- Despite the overwhelming evidence of clozapine’s superior efficacy → Clozapine is underutilized in the USA.
  - Utilization rate is much lower than the estimated prevalence of treatment-resistant schizophrenia.
  - Use of clozapine in the US has been declining: 11% of all antipsychotic prescriptions in 1999 → 4% in 2008.
  - more frequently used in other countries
  - Rather than 3rd trial, often over 5 failed drug trials before clozapine is initiated.

- Barriers include:
  - Systems: Coordination of care within health systems/ Lack of centralized resources/Administrative burden and registry/transportation and service coordination
  - Medical: medical risks and side effects/scarcity of psychiatric services/side effect monitoring
  - Attitudes and education: misunderstanding of treatment algorithm, perceived risks

Kelly et al., 2017
% of all antipsychotic prescriptions for clozapine in people with schizophrenia

Clozapine Utilization Across Nations

Australia | China | Taiwan | England | Sweden | Germany | Korea | Hong Kong | Denmark | Malaysia | USA

Steve Linde/Alamy Live News

The Psychiatric 'Wonder Drug' That Almost No One Is Using

Clozapine could save the lives of suicidal schizophrenic people who aren't responding to other treatments. So why are so few doctors using it?
## Effectiveness: Hospitalization

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Duration, mo</th>
<th>No. With Events/Total No.</th>
<th>Risk Ratio (95% CI)</th>
<th>Favors</th>
<th>Favors</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castro and Elia, 2007</td>
<td>36</td>
<td>5/13 10/12</td>
<td>0.360 (0.159-0.820)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>.03</td>
</tr>
<tr>
<td>Corley et al., 1999</td>
<td>24</td>
<td>6/49 21/75</td>
<td>0.437 (0.150-1.206)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>.05</td>
</tr>
<tr>
<td>Monnoel et al., 2011</td>
<td>36</td>
<td>10/15 41/113</td>
<td>0.465 (0.251-0.860)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>.02</td>
</tr>
<tr>
<td>Bitter et al., 2013</td>
<td>12</td>
<td>149/730 2335/7482</td>
<td>0.616 (0.531-0.715)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vidgen et al., 2015</td>
<td>12</td>
<td>112/479 514/2440</td>
<td>0.624 (0.527-0.740)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vassileva and Morris, 2010</td>
<td>24</td>
<td>34/126 14/94</td>
<td>0.830 (0.387-1.825)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>.06</td>
</tr>
<tr>
<td>Kim et al., 2008</td>
<td>24</td>
<td>12/25 27/36</td>
<td>0.640 (0.408-1.003)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>.05</td>
</tr>
<tr>
<td>Corley et al., 2003</td>
<td>12</td>
<td>4/41 32/252</td>
<td>0.793 (0.295-2.129)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>.65</td>
</tr>
<tr>
<td>Hengstler et al., 2014</td>
<td>12</td>
<td>122/1312 1140/8737</td>
<td>0.814 (0.711-0.921)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>.003</td>
</tr>
<tr>
<td>Strogd et al., 2016</td>
<td>12</td>
<td>529/2370 643/2170</td>
<td>0.825 (0.748-0.901)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tihonen et al., 2006</td>
<td>9</td>
<td>23/150 75/437</td>
<td>0.893 (0.582-1.372)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>.21</td>
</tr>
<tr>
<td>Gao et al., 2011</td>
<td>12</td>
<td>14/177 58/925</td>
<td>0.915 (0.521-1.609)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>.76</td>
</tr>
<tr>
<td>Law et al., 2006</td>
<td>24</td>
<td>32/63 20/49</td>
<td>0.927 (0.642-1.337)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>.09</td>
</tr>
<tr>
<td>Vosacco et al., 2016</td>
<td>24</td>
<td>113/324 4255/13656</td>
<td>0.954 (0.821-1.110)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>.55</td>
</tr>
<tr>
<td>Herzig et al., 2017</td>
<td>24</td>
<td>27/60 50/107</td>
<td>0.563 (0.368-1.360)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>.36</td>
</tr>
<tr>
<td>Novick et al., 2012</td>
<td>12</td>
<td>49/308 1054/3760</td>
<td>1.138 (0.860-1.544)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>.040</td>
</tr>
<tr>
<td>Herzig et al., 2018</td>
<td>24</td>
<td>6/13 15/90</td>
<td>1.210 (0.613-2.411)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>.38</td>
</tr>
<tr>
<td>Williams et al., 2006</td>
<td>24</td>
<td>12/31 28/166</td>
<td>1.395 (0.798-2.439)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>.28</td>
</tr>
<tr>
<td>Taylor et al., 2008</td>
<td>21</td>
<td>14/40 88/360</td>
<td>1.432 (0.904-2.247)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>.13</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1375/7073 10853/42380</td>
<td>0.817 (0.725-0.920)</td>
<td>Clozapine</td>
<td>NC, Sams</td>
<td>.001</td>
</tr>
</tbody>
</table>

NNT: 18 (95% CI, 12-40)  
Heterogeneity: P = .87 %, I² = .001

---

## Effectiveness

All-Cause Mortality Rates During Current Clozapine Treatment, During Intervals of No Clozapine Treatment, and After Clozapine Discontinuation

![Mortality Rates Graph](image)

Masuda et al., 2019

Wimberley et al., 2017
Study Objectives

• Little work has described real-world outcomes of clozapine treatment within communities.

• What is the impact of clozapine use in Allegheny County?
  • How does clozapine use change service utilization?

Study Objectives

• a retrospective, mirror-image examination of clozapine treatment in relation to utilization of community-based resources.

• We focused on publicly funded, behavioral health and human services data in Allegheny County,

• The present study had two aims:
  • 1) to characterize utilization across a variety of measures before and after CLZ initiation, and
  • 2) apply data-driven methods to explore patterns and predictors of engagement across service in clozapine treated individuals.

• Given CLZ’s superior efficacy, we hypothesized an overall decrease in use of emergent services, coupled with an increase in services focused on functional recovery and psychosocial support.
Methods

- Allegheny County Data Warehouse
- Clozapine initiation for patients who initiated clozapine between 2009 to 2016 had no history of clozapine for at least one year prior.
- ages 18-65;
- diagnosis of schizophrenia or schizoaffective disorder;
- at least 80% (144 days) of clozapine coverage during initiation phase.
- compare 180 before initiation vs. 180 days after the initiation period
Methods

- Mirror image comparisons across service use category (before vs. after via Chi square)
- K Means clustering – data driven analysis of patterns of utilization
- Logistic regression – examine if compliance/CLZ use predicted service utilization in whole sample (N=266)

Demographics

- N=266 total; N=163 with 80% claims of clozapine during initiation period.
- Age = 40.34 ± 12.5 years
- Male 57%, Female 43%
- Race:
  - White 55.8%,
  - Black/African American 41.7%
  - Asian 1.8%
Results

**BH service utilization 180 days pre-post clozapine episode**

*P < 0.05, Bonferroni Corrected

---

Results
Results

Clustering Results
Results: logistic regression

- Exploratory analyses examined the whole cohort (N=266) to see if adherence during initiation phase predicted outcomes during follow-up period:
  - Examined inpatient and outpatient care

- Preliminarily see that greater adherence predicts:
  - Less hospitalizations

Conclusions

- Clozapine is underutilized in Allegheny County

- Successful clozapine use is associated with
  - Less emergent care/inpatient hospitalizations
  - Greater use of services focused on community re-engagement.

- There may be patterns of community service utilization driven by age and other factors
  - Should we personalize treatment planning based on these measures?

- Adherence is key for successful outcomes.
Acknowledgements

University of Pittsburgh

- Peter Jhon
- Kaiqi Bian
- Kangho Suh
- Jessica Gannon
- Roy Chengappa
- STEP/CRS
- Patients & their families