Clozapine – a few points

James L Roerig PharmD, BCPP
Professor
Director Undergraduate Medical Education in Psychiatry & Psychiatry Clerkship
Assistant Director Psychiatry Residency Program
Department of Psychiatry and Behavioral Science
University of North Dakota School of Medicine and Health Sciences
Exacerbation in behavior that consists of pushing staff, pounding on doors, screaming, stating “I am going to die”, refusing tasks and ADLs. His affect is described in the record as irritable, dysphoric and labile. His thought process is described as tangential and over inclusive. He complains of “voices in his head” and demonstrates ideas of reference. He is reported to be dressing in layers of clothes.

Divalproex 4000 mg
Haloperidol 4 mg AM, 2 mg HS
Olanzapine 10 mg BID
Aripiprazole 30 mg qd
Lorazepam 1 mg tid
Trihexyphenidyl 2 mg BID
Hydroxyzine 100 mg HS

Clozapine 250 mg/d
Divalproex 3000 mg

Doing better then he ever has!
John Paulsen

Funeral services for John M. Paulsen, who died Friday, will be held at 2 pm Monday in First Presbyterian Church of Fargo.

John Miller Paulsen was born in Fargo on March 30, 1956, the son of Mr. and Mrs. John Q. Paulsen.

John attended Clara Barton Elementary School and graduated from Fargo South in 1973. While there, he was a member of South High School Varsity Swimming Team.

During his high school years, John developed schizophrenia and for the next 20 years was treated and hospitalized almost continuously for his illness. In approximately 1991, when the drug Clozapine became available for use in the United States, John's illness became much more readily treatable and his life became so much happier.

He was able to be discharged from hospitals and never had to return. He lived in his own apartment, managed his own affairs, worked part time at Herbergers in Moorhead and as a volunteer at First Presbyterian church.

His mother, Margo, died on October 14, 1996. He is survived by his father, his brother, Jim, Jim's wife Kim, both of Kansas City, Missouri, his niece and nephew, Hannah and John Paulsen of Kansas City, and by his sister, Jean of Eagan, Minnesota.

He will be missed by family and friends who loved him very much.

Memorials to Southeast Human Services or First Presbyterian Church of Fargo will be welcomed.
Point 1

First of the atypical antipsychotics to be developed

- 1971 - first introduced in Europe
- 1975 - 16 cases of Agranulocytosis in Finland
  - 8 died of complications
- 1989 - FDA approval (marketed in 1990) for treating treatment-resistant schizophrenia
Clozapine Overview

- Requires regular absolute neutrophil counts
  - Weekly – first 6 months
  - Bi-weekly – second 6 months
  - Monthly – for duration of treatment
- Troponin levels
  - Weekly – first 4 weeks
Discontinuation of clozapine without rechallenge

- Agranulocytosis
- Myocarditis
- Cardiomyopathy
- QTc interval > 500 milliseconds
  - (appropriate correction method)

Nielsen et al. 2013
Clozapine discontinuation with potential rechallenge

- Ileus or subileus
- Neuroleptic malignant syndrome
- Venous thromboembolism
- Diabetic ketoacidosis or hyperosmolar coma

Nielsen et al. 2013
Do not generally warrant clozapine discontinuation - but management

- Neutropenia
- Leukocytosis
- Seizures
- Orthostatic hypotension
- Severe constipation
- Weight gain and metabolic abnormalities
- Moderately prolonged myocardial repolarization

Nielsen et al. 2013
Rarely lead to clozapine discontinuation

- Eosinophilia
- Leukocytosis
- Drug-induced fever
- Tachycardia

Provided that myocarditis and neuroleptic malignant syndrome are ruled out

Nielsen et al. 2013
Tiihonen et al. 2009

- Results
  - Compared with current use of perphenazine
    - Highest risk for overall mortality
      - Quetiapine (adjusted hazard ratio [HR] 1.41, 95% CI 1.09–1.82)
    - Lowest risk for overall mortality
      - Clozapine (0.74, 0.60–0.91; p=0.0045 clozapine vs perphenazine p<0.0001 for all other antipsychotic drugs)
Clozapine uses

1. **FDA Indication** - Treatment of Refractory Schizophrenia

2. **FDA Indication** - Reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder

3. Violent, Aggressive Patients

4. Patients With Tardive Dyskinesia
Point 2

- Does clozapine work?
- Does it work better than other antipsychotics
Efficacy-Refractory Schizophrenia

- Unsurpassed efficacy, has not been matched over the twenty three years it has been on the market
  
  Hill & Freudenreich, et al. 2013

- Displays neurotrophic and neurogenetic properties

  Pedrini et al. 2001; Halim et al. 2004; Noriyoshi et al. 2006; Maeda et al. 2007
A priori Response – 20% Reduction in BPRS

% Responders at 6 weeks

30

P<.001

35

25

20

15

10

5

0

Clozapine

Chlorpromazine

Kane et al. 1988
McEvoy et al. 2006

clozapine > quetiapine or risperidone but not olanzapine

Catie Study
Change in PANSS Score

Clozapine
Olanzapine

McEvoy et al. 2006
Leucht et al. 2013

- Bayesian-framework, multiple-treatments meta-analysis
- Randomized controlled trials compare 15 antipsychotic drugs and placebo
- Acute treatment of schizophrenia
  - Not treatment refractory
- 212 suitable trials
  - 43,049 participants
Figure 3: Forest plot for efficacy of antipsychotics drugs compared with placebo
Treatments are ranked according to their surface under the cumulative ranking (SUCRA) values (appendix p 98).
SMD=standardised mean difference. CrI=credible interval.
Samara et al. 2016

- Published and unpublished single and double-blind RCTs in treatment-resistant schizophrenia
- Compared any antipsychotic with another antipsychotic or placebo
  - At any dose and in any form of administration
- Forty blinded RCTs
  - 5172 participants
• Little evidence of the superiority of clozapine

• Studies not included:
  • Essock et al. 2000
  • CATIE (McEvoy et al. 2006)
  • CUTLASS 2 (Lewis et al. 2006)
Samara et al. 2016
Vanasse et al. 2016

- Compared, in a real-world setting
  - Risk of mental health events
  - Risk physical health events
- Different antipsychotic drugs
  - Clozapine
  - Olanzapine
  - Risperidone
  - Quetiapine
  - First-generation antipsychotics
- 18,869 adult patients
- Increased risk of mental and physical health events
  - Quetiapine
  - Not using any antipsychotics
- Confirmation of better performance of clozapine
Vanasse et al. 2016
Vanasse et al. 2016
Vanasse et al. 2016

(a) INTENT-TO-TREAT ANALYSIS

CLOZ
OLAN  Risk of discontinuation of any AP treatment
RISP
QUET

0.2  0.4  0.5  0.67  1.0  1.5
FGAs worse HR

(c) INTENT-TO-TREAT ANALYSIS

CLOZ
OLAN  Risk of discontinuation, switching or adding AP treatment
RISP
QUET

0.4  0.5  0.67  1.0  1.5  2.0  2.5
FGAs worse HR FGAs better
Efficacy – Suicide

Meta-analysis

Clozapine associated with a 3 fold lower risk of suicidal behavior vs. other antipsychotics

Hennen & Baldessarini 2005
Efficacy-Violent, Aggressive Patients

- Violent, aggressive patients
  - 112 week, double blind trial comparing clozapine, olanzapine and haloperidol, for reducing violent behaviors in physically assaultive patients with schizophrenia or schizoaffective disorder
- Clozapine superior to other drugs
  - Reducing number of physical assaults
  - Reducing the severity of physical assaults
  - Reducing overall aggression

Krakowski et al. 2006
Efficacy-Tardive Dyskinesia

- Data suggest that dyskinetic symptoms decrease, along with dopaminergic hypersensitivity, with long-term clozapine treatment
  Lieberman et al., 1991; 2007

- Several open trials and case series or case reports suggest a beneficial effect of clozapine on existing TD

- Especially beneficial in those patients in which TD is combined with tardive dystonia
  Louza and Bassitt, 2005; van Harten et al., 1996,
Does clozapine work?

Yes! and better than anything you can prescribe currently and for some time into the future
Point 3

- Clozapine Non-use
Clozapine Non-use

- CATIE study
  - Only 85 of 318 (27%) who had inadequate therapeutic effect entered the phase 2 clozapine trial
    McEvoy et al. 2006

- The use of clozapine has been declining in the US
  - Prescriptions dropped from 11% in 1999 to 5% in 2002
    Kelly & Buchanan 2007

- Veterans Health Administration – 2% receiving clozapine
  Taylor et al. 2003

- Delay of 5 years before initiating clozapine
  - Reassessment nine years later found the delay of 4 years
    Taylor et al 2003; Howes et al. 2010
Clozapine Non-use

- Additional risk to the patient of not using clozapine
  - Polypharmacy, high doses
  - Poor functioning
  - Frequent hospitalizations
  - Increased risk of suicide

Meltzer 2003