Agranulocytosis in clozapine: myths and facts

Dr. P.F.J. Schulte, psychiatrist
Mental Health Services Noord-Holland-Noord
Alkmaar, Netherlands
Statement of Potential Conflicts of Interest

Agranulocytosis in clozapine: myths and facts

Relating to this presentation, there are no relationships that could be perceived as potential conflict of interests.
Outline

- History and some facts
- Mortality in clozapine users
- Appraisal of WBC results
- Rechallenge after leukopenia
- Termination of WBC controls

For all remaining questions:
Dutch Clozapine Guideline (in English) at:
www.clozapinepluswerkgroep.nl
Agranulocytosis: history and facts

- Incidence of agranulocytosis in Europe before mandatory WBC controls: 1 to 2% per year#
- Incidence of agranulocytosis in clinical research for registration in the US (1989): 1.3% in the first year*
- Mortality of agranulocytosis before 1989: 32%* (now 3-4%)
- Mortality in unexpected agranulocytosis: 16%
- Mortality caused by clozapine agranulocytosis (with controls): 1:10,000 (US) en 1:26,000 (GB)

*United States package insert
Mortality in current clozapine users vs. past clozapine users

- 67,072 current and former clozapine users
- 85,399 person-years
- Lower mortality in current users
- Suicides per year: 0.039% vs. 0.219% (RR 5.67)

Risk of death from any cause

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of deaths</th>
<th>Person-years</th>
<th>Mortality</th>
<th>Crude rate ratio (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>182</td>
<td>32000</td>
<td>5.69</td>
<td>0.53 (0.43-0.65)</td>
<td>0.74 (0.60-0.91)</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>193</td>
<td>17930</td>
<td>10.77</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>1481</td>
<td>132320</td>
<td>11.19</td>
<td>1.04 (0.89-1.21)</td>
<td>1.08 (0.92-1.26)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>264</td>
<td>25130</td>
<td>10.50</td>
<td>0.98 (0.81-1.17)</td>
<td>1.13 (0.93-1.36)</td>
</tr>
<tr>
<td>Thoridazine</td>
<td>227</td>
<td>18420</td>
<td>12.32</td>
<td>1.14 (0.94-1.39)</td>
<td>1.14 (0.93-1.38)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>295</td>
<td>19410</td>
<td>15.20</td>
<td>1.41 (1.18-1.69)</td>
<td>1.34 (1.12-1.62)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>135</td>
<td>7040</td>
<td>19.19</td>
<td>1.78 (1.43-2.22)</td>
<td>1.37 (1.10-1.72)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>89</td>
<td>5360</td>
<td>16.60</td>
<td>1.54 (1.20-1.98)</td>
<td>1.41 (1.09-1.82)</td>
</tr>
<tr>
<td>Other</td>
<td>1234</td>
<td>70520</td>
<td>17.50</td>
<td>1.63 (1.40-1.89)</td>
<td>1.45 (1.24-1.69)</td>
</tr>
</tbody>
</table>

Risk of death from any cause

Risk of death from suicide

Adjusted HR (95% CI)
### Risk of death from any cause

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of deaths</th>
<th>Person-years</th>
<th>Mortality*</th>
<th>Crude rate ratio (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>182</td>
<td>32,000</td>
<td>5.69</td>
<td>0.53 (0.43-0.65)</td>
<td>0.74 (0.60-0.91)</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>193</td>
<td>17,930</td>
<td>10.77</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>1,481</td>
<td>132,320</td>
<td>11.19</td>
<td>1.04 (0.89-1.21)</td>
<td>1.08 (0.92-1.26)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>264</td>
<td>25,130</td>
<td>10.50</td>
<td>0.98 (0.81-1.17)</td>
<td>1.13 (0.93-1.36)</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>227</td>
<td>18,420</td>
<td>12.32</td>
<td>1.14 (0.94-1.39)</td>
<td>1.14 (0.93-1.38)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>295</td>
<td>19,410</td>
<td>15.20</td>
<td>1.41 (1.18-1.69)</td>
<td>1.34 (1.12-1.62)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>135</td>
<td>70,400</td>
<td>19.19</td>
<td>1.78 (1.43-2.22)</td>
<td>1.37 (1.10-1.72)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>89</td>
<td>53,600</td>
<td>16.60</td>
<td>1.54 (1.20-1.98)</td>
<td>1.41 (1.09-1.82)</td>
</tr>
<tr>
<td>Other</td>
<td>1,234</td>
<td>70,520</td>
<td>17.50</td>
<td>1.63 (1.40-1.89)</td>
<td>1.45 (1.24-1.69)</td>
</tr>
</tbody>
</table>

### Risk of death from suicide

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of deaths</th>
<th>Person-years</th>
<th>Mortality*</th>
<th>Crude rate ratio (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>27</td>
<td>32,000</td>
<td>0.84</td>
<td>0.46 (0.28-0.76)</td>
<td>0.34 (0.20-0.57)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>7</td>
<td>70,400</td>
<td>1.00</td>
<td>0.54 (0.24-1.22)</td>
<td>0.61 (0.27-1.37)</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>226</td>
<td>132,320</td>
<td>1.71</td>
<td>0.93 (0.64-1.34)</td>
<td>0.86 (0.59-1.24)</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>27</td>
<td>18,420</td>
<td>1.47</td>
<td>0.80 (0.48-1.32)</td>
<td>0.93 (0.56-1.55)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>57</td>
<td>25,130</td>
<td>2.27</td>
<td>1.23 (0.80-1.89)</td>
<td>0.94 (0.61-1.45)</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>33</td>
<td>17,930</td>
<td>1.84</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Risperidone</td>
<td>47</td>
<td>19,410</td>
<td>2.42</td>
<td>1.32 (0.84-2.05)</td>
<td>1.12 (0.72-1.76)</td>
</tr>
<tr>
<td>Other</td>
<td>194</td>
<td>70,520</td>
<td>2.75</td>
<td>1.49 (1.03-2.16)</td>
<td>1.55 (1.07-2.25)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>19</td>
<td>53,600</td>
<td>3.54</td>
<td>1.93 (1.09-3.39)</td>
<td>1.58 (0.89-2.79)</td>
</tr>
</tbody>
</table>

### Risk of death from ischaemic heart disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of deaths</th>
<th>Person-years</th>
<th>Mortality*</th>
<th>Crude rate ratio (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>42</td>
<td>32,000</td>
<td>1.31</td>
<td>0.25 (0.17-0.35)</td>
<td>0.78 (0.54-1.12)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>21</td>
<td>53,600</td>
<td>3.92</td>
<td>0.73 (0.46-1.17)</td>
<td>0.83 (0.52-1.34)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>65</td>
<td>25,130</td>
<td>2.59</td>
<td>0.48 (0.35-0.66)</td>
<td>0.88 (0.63-1.21)</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>104</td>
<td>18,420</td>
<td>5.65</td>
<td>1.05 (0.80-1.39)</td>
<td>0.97 (0.73-1.29)</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>522</td>
<td>132,320</td>
<td>3.94</td>
<td>0.74 (0.59-0.92)</td>
<td>0.97 (0.77-1.21)</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>96</td>
<td>17,930</td>
<td>5.35</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Risperidone</td>
<td>119</td>
<td>19,410</td>
<td>6.13</td>
<td>1.15 (0.88-1.50)</td>
<td>1.17 (0.89-1.54)</td>
</tr>
<tr>
<td>Other</td>
<td>520</td>
<td>70,520</td>
<td>7.37</td>
<td>1.38 (1.11-1.71)</td>
<td>1.21 (0.97-1.51)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>72</td>
<td>70,400</td>
<td>10.23</td>
<td>1.91 (1.41-2.59)</td>
<td>1.24 (0.91-1.69)</td>
</tr>
</tbody>
</table>
Possible confounders

- 14,754 individuals with SMI
- 879 deaths
- Mortality clozapine vs. non-clozapine after adjustment: hazard ratio 0.4 (95% CI 0.2-0.7)
- Mortality clozapine vs. olanzapine after adjustment: hazard ratio 0.4 (95% CI 0.2-0.8)
- True for natural and unnatural causes of death

Hayes et al. Schiz Bull 2014, in press
Types of low WBC counts

- Measurement or reporting error
- Circadian rhythm
- Benign ethnic neutropenia
- Benign clozapine leukopenia (transient peripheral destruction; Hummer et al. 1992: 8/68 patients)
- Malign leukopenia leading to agranulocytosis
**Benign Ethnic Neutropenia (BEN)**

<table>
<thead>
<tr>
<th></th>
<th>WBC</th>
<th>Neutrophils</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BEN</td>
<td>Regular</td>
</tr>
<tr>
<td>Normal (green)</td>
<td>&gt; 3,0 x 10^9</td>
<td>&gt; 3,5 x 10^9</td>
</tr>
<tr>
<td>Lowered (amber)</td>
<td>2,5 – 3,0 x 10^9</td>
<td>3,0-3,5 x 10^9</td>
</tr>
<tr>
<td>Agranulocytosis (red)</td>
<td>&lt; 2,5 x 10^9</td>
<td>&lt; 3,0 x 10^9</td>
</tr>
</tbody>
</table>

Normal (green): satisfactory.
Lowered (amber): continuation of clozapine with repeated measurement.
Agranulocytosis (red): immediate cessation of clozapine.

Rajagopal Postgrad Med J 2005
Types of low WBC counts

- Measurement error
- Circadian rhythm
- Benign ethnic neutropenia
- Benign clozapine leukopenia (transient peripheral destruction; Hummer et al. 1992: 8/68 patients)
- Malign leukopenia leading to agranulocytosis
Stages of neutropenia: risks and treatment

- >1000/µl: no significant risk of infection
- 500-1000/µl: some risk of infection, treat fever like normal policlinic patient
- <500/µl (agranulocytosis): high risk of infection, nearly always clinical symptoms. Parenteral antibiotics.
- <200/µl: very high risk of (opportunistic) infections, reverse isolation, broad spectrum antibiotics
Interruption/termination of treatment with clozapine

- **EMA:**
  - stop with
  - Leukocytes $< 3000/μl$ and/or
  - Granulocytes $< 1500/μl$

- **FDA:**
  - interrupt with
  - Leukocytes $< 3000/μl$ and/or
  - Granulocytes $< 1500/μl$
  - stop with
  - Leukocytes $< 2000/μl$ and/or
  - Granulocytes $< 1000/μl$
Rechallenge

- 17% of rechallenges after leukopenia/granulopenia develop agranulocytosis
- If mortality is set at 5% mortality of rechallenge (without earlier agranulocytosis) is 0.85%
- In the literature positive cases of rechallenge even after agranulocytosis

<table>
<thead>
<tr>
<th></th>
<th>failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia or granulopenia</td>
<td>38% (95% CI 26-52)</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>1 of 1</td>
</tr>
</tbody>
</table>

Rechallenge with Lithium

- All clozapine rechallenges with lithium in one hospital compared to rechallenges from the national clozapine register
- Lithium for 1 or 2 weeks on 0.4mmol/L, then start clozapine
- Failures 21.2% vs. 4%; ARD 29.8% (95% CI 14.6-45.0)
- Unclear whether Lithium really decreases the risk of agranulocytosis
- Advice: do not rechallenge patients with agranulocytosis or severe granulopenia >2 days during the first 18 weeks, except if other possible causes

Rechallenge with Lithium

- All clozapine rechallenges with lithium in one hospital compared to rechallenges from the national clozapine register
- Lithium for 1 or 2 weeks on 0.4 mmol/L, then start clozapine
- Failures 21.2% vs. 4%; ARD 29.8% (95% CI 14.6-45.0)
- Unclear whether lithium really decreases the risk of agranulocytosis
- Advice: do not rechallenge patients with agranulocytosis or severe granulopenia >2 days during the first 18 weeks, except if other possible causes


First, do no harm!
Controls for ever and ever?

- EMA and FDA: monthly WBC counts up to four weeks after termination of treatment
- Patients want to stop
Risk of moderate leukopenia and agranulocytosis

US Hazard Rates

Time (wks)
0 5 10 15 20 25 30 35 40 45 50

Hazard rate (per 1000 patient-years)

Hazard rate (Moderate Leukopenia)
Hazard rate (Agranulocytosis)

V. Kumar. FDA.gov
# Incidence per 1000 patient years

<table>
<thead>
<tr>
<th>Country</th>
<th>Severe leucopenia</th>
<th>Agranulocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;18wks</td>
<td>19-52 wks</td>
</tr>
<tr>
<td>USA</td>
<td>6.93</td>
<td>0.48</td>
</tr>
<tr>
<td>GB/Ire</td>
<td>33.5</td>
<td>4.25</td>
</tr>
<tr>
<td>Australia</td>
<td>12.76</td>
<td>1.58</td>
</tr>
</tbody>
</table>

V. Kumar. FDA.gov
Agranulocytosis per 1000 person years

- FGA min.
- FGA max.
- Mianserine
- Calcium-dobesilate
- General population
- Cloz. >6 months
- Cloz. >12 months
- Chloramphenicol
Mortality
per 1000 person years

mortaliteit
Mortality
per 1000 person years
Mortality
per 1000 person years

Mortaliteit
Conclusion

- Mortality GB and US resp. caused by termination of WBC controls after the 1st year: 0.46/1000 and 0.13/1000 patient-years
- If mortality of agranulocytosis is set at 5% and not 16% the risk is 0.15 and 0.04/1000 patient-years
- In the second 6 months of clozapine treatment these risks are about twice as high.

Schulte, Ann Pharmacother 2006;40:683-688
Dutch clozapine guideline

- If a mentally competent and adequately informed patient explicitly wants to stop having routine blood tests, this can be permitted after the first six months of clozapine treatment.

- However, the WBC count must still be monitored immediately if there is any clinical suspicion of agranulocytosis.

- Low frequency tests, for example four times a year, are still advisable.
Clozapine
Medicine of last resort

Do not overestimate the risks
Thank you for your attention!

For all remaining questions:
Dutch Clozapine Guideline (in English) at
www.clozapinepluswerkgroep.nl