
Dan Cohen, psychiatrist
FACT-team Heerhugowaard
North-Holland North, Netherlands, Europe
Disclosure

No conflict of interests

Membership of the Dutch Clozapine Collaboration Group
The special effects of clozapine: when is it time for the drug of last resort?

Grant your patient an adequate trial
Side-effects

a) Uncommon dangerous side-effects:
- definition
- incidence
- detection
- treatment

b) Common & harmless, potentially dangerous side-effects:
- incidence
- detection
- treatment
a. Uncommon dangerous side-effects

Side-effects that are

- uncommon

- emerge during clozapine treatment

- lethal when not timely diagnosed and adequately treated
How lethal are these side effects?

Review of literature between 1990-2010

- Agranulocytosis
- DKA
- GIH
- Myocarditis/cardiomyopathy

Leukopenia and agranulocytosis

1. The first thing that comes to mind.
2. Clozapine’s best studied serious side-effect.
3. This side-effect has negatively affected clozapine prescription
# Leukopenia and agranulocytosis: the cut-off points

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>UK</th>
<th>Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate leukopenia</strong></td>
<td>WBC ≤ 3000</td>
<td>WBC ≤ 3000 or ANC &lt; 2000</td>
<td>WBC ≤ 3000</td>
</tr>
<tr>
<td><strong>Severe leukopenia</strong></td>
<td>WBC &lt; 2000</td>
<td>WBC &lt; 2000 or ANC &lt; 1000</td>
<td>WBC &lt; 2000</td>
</tr>
<tr>
<td><strong>Agranulocytosis</strong></td>
<td>WBC ≤ 1000 or ANC ≤ 500</td>
<td>WBC ≤ 1000 or ANC &lt; 500</td>
<td>WBC ≤ 1000 or ANC ≤ 500</td>
</tr>
</tbody>
</table>

WBC: white blood cell count  
ANC: absolute neutrophil count
Differential diagnosis of leukopenia

1. Benign ethnic neutropenia (BEN)
2. Intercurrent bacterial or viral infection
3. Diurnal variation: leucocytes counts in blood shows a diurnal variation: lowest in the morning, highest in the afternoon
Benign Ethnic Neutropenia

**Definition**
Lower mean white blood cell (WBC) count without any signs of illness = lower WBC count in the normal, healthy population.

**Population**
People of African, Caribbean or Middle-Eastern origin
### BEN: cut-off points

<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>Green (=satisfactory WBC)</td>
<td>&gt; 3,0 x 10⁹</td>
<td>&gt; 3,5 x 10⁹</td>
</tr>
<tr>
<td>Amber (repeat WBC)</td>
<td>2,5 – 3,0 x 10⁹</td>
<td>3,0-3,5 x 10⁹</td>
</tr>
<tr>
<td>Red (= immediate cessation of clozapine)</td>
<td>&lt; 2,5 x 10⁹</td>
<td>&lt; 3,0 x 10⁹</td>
</tr>
</tbody>
</table>

Rajagopal Postgrad Med J 2005
Intercurrent infection

(Patho-)physiology

- Initial phase of infection
- Increased adherence of leucocytes to the vascular wall
- Leucocytes crossing the vascular wall
- Leucocyte migration towards the infected cell
- Death of leucocytes

Result: lowered WBC plasma level = lowered WBC count

Only later will infection result in increased production and levels of leucocytes (= leukocytosis)
Diurnal variation:

- leucocytes counts in blood show diurnal variation
- lowest in the morning, highest in the afternoon

Advise after the first leukopenia:

- Rule out a mistake -> repeat WBC count from morning blood sample
- Rule out diurnal variation -> WBC count from afternoon sample
Agranulocytosis

- Onset: 80-85% in the initial first 6 months

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>Affected cases</td>
</tr>
<tr>
<td>3.8‰ – 8.0‰</td>
<td>2.2% - 4.2%</td>
</tr>
<tr>
<td>0.1‰ – 0.3‰</td>
<td>2.2% - 4.2%</td>
</tr>
</tbody>
</table>

Treatment emergent agranulocytosis: general recommendation

1. Establish a working alliance with an internist and/or hematologist **before initiation of clozapine treatment**, whom you can consult if necessary.

2. When leukopenia emerges, consult the internist/hematologist.
a. Other uncommon serious side-effects

- Diabetic Keto-Acidosis (DKA)
- Gastro-Intestinal Hypomotility (GIH)
- Myocarditis
Diabetic Keto-Acidosis (DKA)

- Rarely occurring severe disruption of the glucose homeostasis or severe worsening of pre-existing DM
- Cause: acute shortage of insulin
- Pathophysiological mechanisms are unclear
Diabetic Keto-Acidosis (DKA)

Outcome:
- metabolic acidosis
- metabolic ketosis
- if undetected and therefore untreated: coma and death
DKA

• Reported cases occurred most frequently with olanzapine or clozapine.

But

• Cases have been reported with all atypical antipsychotics:
  - Aripiprazole
  - Risperidone
  - Quetiapine
  - Ziprasidone
DKA in clozapine treatment

- Onset seems to be restricted to the initial 3 months of treatment
- Diagnosis may occur later, after the hyperglycemia has become more severe and has lead to metabolic complications.

DKA mortality in clozapine treatment

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2‰ - 3.1‰</td>
<td>0.2‰ - 4.4‰</td>
</tr>
</tbody>
</table>

Myocarditis

- Onset: restricted to the initial 1 month of treatment

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Australia</strong></td>
<td><strong>Total population</strong></td>
</tr>
<tr>
<td>7,0‰ – 34.0‰</td>
<td>0‰ - 1,2‰</td>
</tr>
<tr>
<td><strong>Rest of world</strong></td>
<td>0,07‰ – 0,6‰</td>
</tr>
</tbody>
</table>
b. Common & harmless: the case of constipation

- Constipation occurs in 25.1% of clozapine-treated patients.
- Danger: severe constipation can result in (sub-)ileus and eventually death.

- Meltzer InterSept Trial. Arch Gen Psychiatry 2003
Risk factors of GIH

1. Co-medication.
   Anticholinergic drugs or other drugs that cause constipation.

   **Caveat**
   Medication is co-medication only in the eyes of the treating psychiatrist, but clozapine might be considered as comedication by the GP or somatic specialist.
Risk factors of GIH

2. Dosage: more risk with higher dosage

3. Treatment duration: conflicting results.
   - initial phase: 36% < 4 months, 50% < 1 year (Palmer)
   - maintenance phase: mean duration 1528 days (Nielsen)

## GIH: (sub-)ileus

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>Affected cases</td>
</tr>
<tr>
<td>4% - 8%</td>
<td>0,98% - 1,19%</td>
</tr>
</tbody>
</table>
Comparison of incidence (‰) & mortality rates of all 4 dangerous side effects of clozapine.

<table>
<thead>
<tr>
<th></th>
<th>Incidence</th>
<th>Mortality</th>
<th>Incident cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total population (‰)</td>
<td>Total population (‰)</td>
<td></td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>3,8 – 8,0‰</td>
<td>0,1 - 0,3‰</td>
<td>2,2- 4,2%</td>
</tr>
<tr>
<td>DKA</td>
<td>1,2 - 3,1‰</td>
<td>0,2 - 4,4‰</td>
<td>20,0- 31,0%</td>
</tr>
<tr>
<td>GIH</td>
<td>4,0 - 8,0‰</td>
<td>0,98-1,19‰</td>
<td>15,0-27,5 %</td>
</tr>
<tr>
<td>Myocarditis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>7,0 – 34,0‰</td>
<td>0-1,2‰</td>
<td>0-13%</td>
</tr>
<tr>
<td>Rest of the world</td>
<td>0,07 -0,6‰</td>
<td>0-0,2‰</td>
<td>0-68%</td>
</tr>
</tbody>
</table>

Uncommon serious side-effects: agranulocytosis

In general, psychiatrists are excessively worried over the chances and risks of agranulocytosis.

They tend to be less worried about - some even unaware of other serious side effects.

Both positions are wrong.
Incidence and mortality of agranulocytosis put into perspective

### Incidence

<table>
<thead>
<tr>
<th>Country</th>
<th>Study pop</th>
<th>Agranulocytosis</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>N=99,500</td>
<td>382 cases</td>
<td>0.382%</td>
</tr>
<tr>
<td>Australia</td>
<td>N=11,000</td>
<td>33 cases</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

In the US-study, 12 patients died.

Honigfeld J Clin Psych 1998; Drews Australasian Psych 2013
Incidence and mortality of agranulocytosis put into perspective

**Mortality rate**

- Affected population (12/382) = 3.14%
- Total population (12/99,500) = 0.1‰ (= 1:10,000 patients)

Honigfeld J Clin Psych 1998
Conclusion

Within the framework of mandatory WBC monitoring, the risk of agranulocytosis is low & kept within acceptable borders.
Obligatory WBC-count has shown to be effective in preventing death as complications of agranulocytosis.

What about the other 3 serious side-effects?
Screening advise for DKA, GIH and myocarditis

Aim: reducing the current high mortality rates to the one of agranulocytosis
Screening advise DKA

- Baseline measurement of fasting plasma glucose (FPG)
- Monthly FPG measurement during the months at risk
  = the first 3 months of clozapine treatment
- Thereafter: yearly measurement of FPG
Screening advice DKA: the role of HbA1c

HbA1c is

- a reliable predictor of long term DM complications
- a reflection of the mean plasma glucose of the previous 2 months
- therefore unsuitable for detection of the rapidly developing new-onset DM/DKA, that may occur in the initial phase of clozapine treatment
Screening advise GIH: two options and one obligation:

Two options

1. Patients defecation pattern is a standard topic at every visit.
2. Preventive prescription of macrocol laxative in all clozapine-treated patients.

One obligation:

Warn and inform the GP on the risk of GIH in clozapine and the possible adverse side-effect of somatic (co-)medication.
Screening advise myocarditis

1. For reasons unknown, myocarditis in clozapine treatment is mainly a problem of Australia and New-Zealand.

2. There is no evidence that warrants routinely monitoring of treatment emergent myocarditis outside Australia and New-Zealand.
Grant your patients a **safe** treatment with clozapine!

The special effect of **clozapine**: what is the right moment for prescription of this drug of last resort?
Thank you for your attention!

d.cohen@ggz-nhn.nl
Questions?
Irrational prescribers’ fear

What is the prove for this statement?
## 1. Delay of initiating clozapine treatment

### Main duration of illness

<table>
<thead>
<tr>
<th></th>
<th>Taylor</th>
<th>Howes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>15</td>
<td>8.6</td>
</tr>
</tbody>
</table>

### Main number of antipsychotic episodes

<table>
<thead>
<tr>
<th></th>
<th>Taylor</th>
<th>Howes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodes</td>
<td>9.2</td>
<td>5.6</td>
</tr>
</tbody>
</table>

### Main theoretical delay of treatment with clozapine

<table>
<thead>
<tr>
<th></th>
<th>Taylor</th>
<th>Howes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>
Remember:
Treatment indications – registered (on-label)

1. Therapy resistant schizophrenia, defined as at least two treatments with other antipsychotic drugs, of which at least one was atypical,
   a) were unsuccessful or
   b) lead to intolerable neurological side-effects.
Maybe it is only a British problem? prescription level in the USA

Study population:
- 1003 VA-patients with schizophrenia or SA disorder
- 46 patients were documented therapy-resistant and qualified for clozapine initiation.

Question: how many were being prescribed clozapine?
Maybe it is only a British problem? prescription level in the USA

Guess what: 1 patient only, amounting to $1/46 = 2.2\%$!

This leaves $97.8\%$ of therapy-resistant patients who qualified, according to all international studies and standards, without clozapine.

NB: in all, clozapine was prescribed to 18 patients = $1.8\%$

In 17 patients clozapine was the second antipsychotic drug, presumably for suicidality or aggression.

Goren et al. Psych Serv 2013
1. Delay of initiating clozapine treatment?

Yes, there is a serious delay and/or reluctance of prescribing clozapine, both in Great-Britain and in the USA.
2. Doubts on compliance with clozapine

Fear for non-compliance in clozapine treated patients is often voiced.

Question: is this fear evidence-based and what exactly is its evidence?
Treatment-compliance (days)

Blacks | Latinos | Whites
---|---|---
1422 | 1659 | 1228
720 | 895 | 812
459 | 566 | 639

Non-clozapine (N=1378)
All antipsychotics (N=2147)
Clozapine (N=749)

Horvits-Lennon Psych Serv 2013
Doubts on compliance with clozapine

Answer:

Fear for non-compliance with clozapine is irrational as it goes against the available evidence.
Obstacles to clozapine treatment

1. Irrational fear of the prescriber.
2. Fear of discussing the possibility of serious, treatment emergent side effects and the resulting obligations of intensive monitoring.
3. Lack of knowledge of side-effects and how to cope with them.
Treatment recommendations

Invest - before prescription - much time in informing the patient and his/her support system of the possible benefits and side-effects of clozapine therapy.
Treatment recommendation: investment of time

Explanation:

1. Treatment-adherence is crucial for successful treatment.

2. Treatment adherence implies daily intake of the prescribed medication. Adherence requires therefore both the patients’ discipline and motivation.

3. Unanswered questions and/or doubts might demotivate and/or undermine patients’ treatment adherence.
2. Emphasize the necessity for intensive monitoring of possible severe, treatment-emergent side effects.
Safeguarding patient’s cooperation

Safe treatment requires cooperative patients who invest their time to comply with the intensive monitoring requirements.
Patient-doctor relation:
confidence goes by foot, but leaves on a horse.

Good doctors
- explain the risks of their treatment
- are well prepared for this possibility
- explain how they will cope when such a side effects occurs
1. Patients are therapy-resistant, so there is no need to rush.

2. It is the outcome, symptom reduction by adequately dosed clozapine, *not the speed* that counts. The main vehicle to attain this outcome is to secure patients’ compliance.

3. Fast dose increases are more dangerous: increased risk of sedation, severe hypotension and seizures.

4. There is no evidence-based treatment option for clozapine-resistant patients.
Start low, go slow:

**een casus**

**Given situation**

A 45-year old female patient with therapy-resistant desorganised schizophrenia. Actually, this impairs any conversation with her.

**Start clozapine therapy:** collapsed after intake of initial dose of 25 mg clozapine. Dose was reduced to 6,25 mg capsules.

**Speed of dose increase:** 1 capsules of 6,25 mg/week. A therapeutic dosage and plasma level was reached after a full year.
Treatment recommendation ‘start low, go slow’: a case report: evaluation after 1 year treatment.

Her functioning improved remarkably:
- she arrived on her own
- in time
- at the outpatient facility
- we were able to have a sensible conversation
- we were able to evaluate the effect of the clozapine on her functioning

All of this had been impossible before clozapine initiation
To confirm my observations, I remarked that her case-manager Rita, who participated in this visit, agreed with me. Hereupon the patient turned to Rita and she asked her: ‘oh, Rita, do you also use clozapine?’
1. Before prescription: invest much time in informing the patient and his/her support system of the possible benefits and side-effects.

2. Emphasize the necessity for intensive monitoring of possible severe, treatment-emergent side effects.

3. Start low, go slow.
Therapeutic drug monitoring (TDM): necessity or luxury?

What do we need TDM for in clozapine treatment?
2. Doubts on compliance with clozapine

‘I always add depot medication to clozapine, as a foundation for antipsychotic therapy. In this way I am always assured of an effective treatment, even when the patient discontinues clozapine.’
TDM and clozapine: the facts

1. Relevant differences exist in pharmacokinetics and -dynamics (absorption, metabolisation, distribution etc.)

2. CYP-1A2, main metabolising liverenzyme, can be inhibited or induced.
   a) inhibited by:
      - caffeine. Coffee, cola and energy drinks (Red Bull and its variants)
      - fluvoxamine (antidepressant) strongly inhibitor of CYP-1A2
   b) induced by:
      - cigarette smoking
      - carbamazepine
TDM and clozapine: the facts.
a therapeutic threshold

1. Patients with plasma-levels < 300-350 ng/l, can be responders or non-responders.

2. Plasma levels of 300-350 ng/l can be an obstacle in non-responders: 30%-60% of non-responders become responders when plasma levels are raised above 300-350 ng/l.

Schulte PFJ. What is an adequate trial of clozapine? Clin Pharmacol 2003
A 42-year old female Caucasian patient with schizophrenia in a sheltered living. Ongoing treatment with a low daily dose of 200 mg clozapine, with adequate plasma level: 490 ng/l.

She develops fever.

What is the differential diagnosis?
Clozapine and infections.

1. Leukopenia or agranulocytosis.  
   *Comment* Highly unlikely. 90%-95% of the cases occur within first 6-12 months of treatment. Chance is ±1/1000, comparable to that with other APs with no obligatory WBC monitoring.

2. Common viral or bacterial infection.  
   *Comment* Yes, why not? Schizophrenia does not protect patients from catching common infections.

Question: so what? what is the importance of infections in clozapine therapy?
The value of TDM in infections

1. Inflammation mediators inhibit clozapine metabolism, resulting in increased plasma levels.

In this case, the laboratory phoned me: her plasma level exceeded the upper limit of 1250 ng/l. Judging by the rise of the curve, the plasma level was estimated at 2000 ng/l.

She showed no clinical signs of intoxication.
The value of TDM in infections: the case of mr. B

2. Quitting smoking – a strong inducer of clozapine metabolism, you remember? - results in increased plasma levels.

Mr. B
A 45-year old Caucasian male out-patient had for years been stable on clozapine. He caught pneumonia and stopped smoking his 20-25 cigarettes/day: they didn’t taste him any more. His consciousness dropped, he went into coma and was admitted at an intensive care unit. He recovered completely.
The value of TDM in infections

2. Quiting smoking (strong inducer of clozapine metabolism), results in increased plasma levels.

Case
A 45-year old Caucasian male out-patient had for years been stable on clozapine. He caught pneumonia and stopped smoking his daily 20-25 cigarettes: they didn’t taste him any more. His consciousness dropped, he went into coma and was admitted at an intensive care unit. He recovered completely.

Cause: two independent mechanisms both resulting in increased clozapine plasma levels.

Schulte PFJ. What is an adequate trial of clozapine? Clin Pharmacol 2003
The value of TDM in non-responders

1. Detection of suboptimal plasma-levels, below 300-350 ng/l.
2. Detection of non-compliance
3. Detection of clozapine intoxication
4. Determination of optimal plasma level and dosage

Schulte PFJ. What is an adequate trial of clozapine? Clin Pharmacol 2003
The value of TDM in infections: take home message

I. When
• inflammation or infection occurs
• a patient decides to quit smoking
Action:
- half the clozapine dosage as long as the cause remains in force.

II. Advise a smoking patient to continue smoking at regular pace. If the patient wants to stop smoking, the first thing to do is to consult the psychiatrist who will lower the dosage of clozapine.
Dutch Clozapine Collaboration Group

Aim

Promotion of clozapine treatment

Activities

1. Online consultation by treating physicians, family members and patients

2. Development of the national clozapine guideline

3. Meetings, accredited by the Dutch Psychiatric Association, for members:
   frequency: 4-6 times/year; plenary lecture; presentation of difficult cases

4. Publications, national and international, on different aspects of clozapine treatment
Dutch Clozapine Collaboration Group

- Independent non-profit organization
- Members: psychiatrists, pharmacists
- Financially independent from
  - government (national, local)
  - health insurances
- Income:
  - membership fee;
  - unrestricted grant from different pharmaceutical companies
Aim
Promotion of clozapine treatment

Activities
1. On line consultation by treating physicians, family members and patients
2. Development of the national clozapine guideline
3. Meetings, accredited by the Dutch Psychiatric Association, for members:
   frequency: 4-6 times/year; plenary lecture; presentation of difficult cases
4. Publications, national and international, on different aspects of clozapine treatment
Questions
Thank you for your attention!

d.cohen@ggz-nhn.nl
Obstacles to clozapine treatment

1. Irrational fear of the prescriber
2. Fear of discussing the possibility of serious, treatment emergent side effects and the resulting obligations of intensive monitoring.
3. Lack of knowledge of side-effects and how to cope with them