Clozapine Case 3: Sertraline 12-24-15

Jose de Leon, MD

3. Clozapine Case 3

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http://www.ncbi.nlm.nih.gov/pubmed/14499324

Educational Objectives

At the conclusion of this presentation, the participant should be able to:

1. Think about pharmacological principles in the context of polypharmacy.
2. Appreciate that for understanding clozapine safety, one must consider:
   - 2.1. Personal, environmental and genetic factors
   - 2.2. Pharmacodynamics and pharmacokinetics.
3. Summarize how to use clozapine levels in clinical practice.
4. Understand the pharmacological mechanisms behind inhibition.

Abbreviations

- ADR: adverse drug reaction
- C: concentration
- C/D ratio: concentration-to-dose ratio
- D: dose
- DDI: drug-drug interaction
- OCD: obsessive-compulsive disorder
- PM: poor metabolizer
- SSRI: selective serotonin reuptake inhibitor
- TDM: therapeutic drug monitoring

Clozapine Case 3

3.0. Introduction

3.1. Clozapine C/D Ratios

3.2. Total Clozapine C/D Ratios

3.3. Pharmacology of Drug Metabolic Inhibition

3.4. SSRIs and Clozapine

3.5. Clinical Relevance of Sertraline-Clozapine DDI

Clozapine Case 3

3.0. Introduction

3.1. Clozapine C/D Ratios

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3.0. Introduction

3.0. Clozapine Case 3: Introduction

- Dr. Pinninti, who was a resident at the time, contacted Dr. de Leon (who at that time knew little about clozapine TDM) regarding a patient on sertraline with high clozapine Cs.
  - 35-yr-old Caucasian ♂ with schizophrenia
  - taking clozapine D: 600 mg/day
- Clozapine TDM was repeated:
  - with sertraline D: 300 mg/day
  - with sertraline D: 150 mg/day
  - after sertraline discontinuation

3.1. Clozapine C/D Ratios

3.1. Clozapine Case 3: Clozapine C/D Ratios

- Taking sertraline 300 mg/day
  - Clozapine D = 600 mg/day
  - Clozapine C = 1300 ng/ml

3.1. Clozapine Case 3: Clozapine C/D Ratios

What was the clozapine C/D ratio on 300 mg/day of sertraline?

3.1. Clozapine Case 3: Clozapine C/D Ratios

What was the clozapine C/D ratio on 300 mg/day of sertraline?

C/D=1300/600=2.2.

3.1. Clozapine Case 3: Clozapine C/D Ratios

Is a clozapine C/D=2.2
normal
in a US Caucasian?

3.1. Clozapine Case 3: Clozapine C/D Ratios

Is a clozapine C/D=2.2
normal
in a US Caucasian?

No, not in Dr. de Leon's experience.

3.1. Clozapine Case 3: Clozapine C/D Ratios

- In US Caucasians, a C/D ratio:
  - >1.2 indicates poor metabolic capacity.
  - <0.6 indicates high metabolic capacity.
  - 0.6-1.2 is probably normal.

  Dr. de Leon is pretty sure of these values.
- In East Asians (Chinese, Koreans and probably Japanese) and CYP2C19 PMs:
  - >2.4 indicates poor metabolic capacity.
  - <1.2 indicates high metabolic capacity.
  - 1.2-2.4 is probably normal.

  These values are based on the literature.

3.1. Clozapine Case 3: Clozapine C/D Ratios

After seeing the prior slide, is a clozapine C/D ratio of 2.2 normal in a Caucasian?

3.1. Clozapine Case 3: Clozapine C/D Ratios

After seeing the prior slide, is a clozapine C/D ratio of 2.2 normal in a Caucasian?

Probably NOT, but you should not trust a single abnormal C.

3.1. Clozapine Case 3: Clozapine C/D Ratios

- On sertraline 150 mg/day:
  - Clozapine D = 600 mg/day
  - Clozapine C = 1400 ng/ml

3.1. Clozapine Case 3: Clozapine C/D Ratios

What was the clozapine C/D ratio on 150 mg/day of sertraline?

3.1. Clozapine Case 3: Clozapine C/D Ratios

What was the clozapine C/D ratio on 150 mg/day of sertraline?

C/D=1400/600=2.3.

3.1. Clozapine Case 3: C/D Ratios

Are repeated clozapine C/D ratios of 2.2 or 2.3 normal in a US Caucasian?

No.

3.1. Clozapine Case 3: Clozapine C/D Ratios

- After sertraline discontinuation:
  - Clozapine D = 600 mg/day
  - Clozapine C = 750 ng/ml

3.1. Clozapine Case 3: Clozapine C/D Ratios

What was the clozapine C/D ratio after sertraline discontinuation?

3.1. Clozapine Case 3: Clozapine C/D Ratios

What was the clozapine C/D ratio after sertraline discontinuation?

C/D=750/650=1.3.

3.1. Clozapine Case 3: Clozapine C/D Ratios

Is a clozapine C/D = 1.3
normal
in a US Caucasian?

3.1. Clozapine Case 3: Clozapine C/D Ratios

Is a clozapine C/D = 1.3
normal
in a US Caucasian?

It is borderline normal.

3.1. Clozapine Case 3: Clozapine C/D Ratios

Do we need to ask any other questions to interpret this C/D ratio?

3.1. Clozapine Case 3: Clozapine C/D Ratios

Do we need to ask any other questions to interpret this C/D ratio?

Yes.

3.1. Clozapine Case 3: Clozapine C/D Ratios

What questions?

3.1. Clozapine Case 3: Clozapine C/D Ratios

Was the patient taking any other medications?

3.1. Clozapine Case 3: Clozapine C/D Ratios

Was the patient taking any other medications?

No.

3.1. Clozapine Case 3: Clozapine C/D Ratios

Was the patient a smoker?

3.1. Clozapine Case 3: Clozapine C/D Ratios

Was the patient
a smoker?

It was not recorded.

3.1. Clozapine Case 3: Clozapine C/D Ratios

Why is smoking status important?

3.1. Clozapine Case 3: Clozapine C/D Ratios

Why is smoking status important?

Smoking is an inducer of clozapine metabolism.

3.1. Clozapine Case 3: Clozapine C/D Ratios

- In US Caucasians:
  - ♀ non-smokers: C/D ratios ≤1.2
  - ♂ smokers: C/D ratios ≥ 0.6
  - ♀ smokers and ♂ smokers: intermediate C/D ratios of 0/6-1.2
- Estimations for East Asians and CYP2C19 PMs:
  - ♀ non-smokers: C/D ratios ≤ 2.4
  - ♂ smokers: C/D ratios ≥ 1.2
  - ♀ smokers and ♂ smokers: intermediate C/D ratios of 1.2-2.4

3.1. Clozapine Case 3: Clozapine C/D Ratios

Was the patient consuming caffeine?

3.1. Clozapine Case 3: Clozapine C/D Ratios

Was the patient consuming caffeine?

It was not recorded.

3.1. Clozapine Case 3: Clozapine C/D Ratios

Why is caffeine intake important?

3.1. Clozapine Case 3: Clozapine C/D Ratios

Why is caffeine intake important?

Caffeine can inhibit clozapine metabolism.

3.2. Total Clozapine C/D Ratios

3.2. Clozapine Case 3: Total C/D Ratios

- Dr. de Leon uses
  - Clozapine C/D ratios for efficacy. Clozapine contributes to efficacy (norclozapine does not).
  - Total clozapine C/D ratios for:
    - studying metabolism. Clozapine metabolism is reflected by norclozapine, too.
    - studying safety: Norclozapine contributes to ADRs.

3.2. Clozapine Case 3: Total C/D Ratios

- This patient also had a ↓ in total clozapine C/D ratio after sertraline discontinuation.

3.2. Clozapine Case 3: Total C/D Ratios

Sertraline	Clo D	C (ng/ml)			C/D ratio	
	mg/day	Clo	NorC	Total	Clo	Total
300	600	1300	520	1820	2.2	3.0
150	600	1400	620	2020	2.3	3.4
0 (5 days)[1]	600	1300	560	1860	2.2	3.1
0(30 days)[2]	600	750	330	1080	1.3	1.8

Clo: clozapine; NorC: norclozapine.

[1]After 5 days sertraline's effects appear to still be present

[2]After 30 days sertraline's effects appear to have disappeared since it is >5 sertraline half-lives.

3.2. Clozapine Case 3: Total C/D Ratios

Summary

	Sertraline	
	On	Discontinued
Clozapine D (mg/day)	600	600
Clozapine C (ng/ml)	≥ 1300	750
Total clozapine C (ng/ml)	≥ 1820	1080
Clozapine C/D	≥ 2.2	1.3
Total clozapine C/D	≥ 3.0	1.8

3.2. Clozapine Case 3: Total C/D Ratios

Sertraline discontinuation was associated with:

↓ in clozapine C,

↓ in total clozapine C,

↓ in clozapine C/D ratio

and

↓ in total clozapine C/D ratio.

3.2. Clozapine Case 3: Total C/D Ratios

↓ in clozapine Cs and C/D ratios are a sign that…?

3.2. Clozapine Case 3: Total C/D Ratios

↓ in clozapine Cs and
C/D ratios are a sign that…?

Sertraline was acting as an inhibitor of clozapine metabolism.

3.2. Clozapine Case 3: Total C/D Ratios

Discontinuation of sertraline was associated with

↑ in clozapine metabolism.

3.2. Clozapine Case 3: Total C/D Ratios

In general,
discontinuing an inhibitor
is associated with
↓ substrate Cs
and
↑ substrate metabolism.

3.3. Pharmacology of Drug Metabolic Inhibition

3.3. Clozapine Case 3: Inhibition

Can sertraline be a CYP inhibitor?

3.3. Clozapine Case 3: Inhibition

Can sertraline be a CYP inhibitor?

Yes.

3.3. Clozapine Case 3: Inhibition

What do you know about pharmacology mechanisms behind

drug metabolic inhibition?

3.3. Clozapine Case 3: Inhibition

- Basic pharmacology articles on inhibition are confusing for clinicians.
- Most articles classify inhibition as:
  - competitive or non-competitive
  - reversible or irreversible
  - or some combination of these categories.
- The next slide provides a simplified version of the literature for clinicians.

3.3. Clozapine Case 3: Inhibition

- Classification of inhibition:
  - irreversible (mechanism-based inhibition)
  - reversible:
    - competitive
    - non-competitive

This is based on a simplification by Dr. de Leon of 2 articles:

http://www.ncbi.nlm.nih.gov/pubmed/18618097

http://www.ncbi.nlm.nih.gov/pubmed/11264468

3.3. Pharmacology of Inhibition

3.3.1. Irreversible Inhibition

3.3.2. Reversible Inhibition

3.3.3. Summary for Psychiatrists

3.3.1. Irreversible Inhibition

3.3.1. Clozapine Case 3: Irreversible Inhibition

- Irreversible means:
  - The enzyme is modified in a irreversible way.
  - New enzyme synthesis is needed to get a functional enzyme.
- Mechanism-based inhibition is a type of irreversible inhibition.

  Pelkonen et al. report that it “can occur via:
  - the formation of metabolite intermediate complexes

    or
  - the strong, covalent binding of reactive intermediates to the
    - protein or
    - heme of the CYP.”

http://www.ncbi.nlm.nih.gov/pubmed/18618097

3.3.1. Clozapine Case 3: Irreversible Inhibition

- Mechanism-based inhibition and psychiatric drugs:
  - Paroxetine is a powerful CYP2D6 inhibitor:
    - Pelkonen et al.'s review describes it as competitive.

      http://www.ncbi.nlm.nih.gov/pubmed/18618097
    - Several studies describes this as mechanism-based inhibition. http://www.ncbi.nlm.nih.gov/pubmed/12584155
    - Dr. de Leon thinks that the clinical data is compatible with the idea that paroxetine is a mechanism-based inhibitor of CYP2D6.
  - Fluoxetine is a powerful CYP2D6 inhibitor, too.
    - In vitro studies are more confusing than in paroxetine.
    - Dr. de Leon thinks that the clinical data shows fluoxetine as similar to paroxetine for CYP2D6 inhibition, but fluoxetine is a relevant inhibitor of other CYPs.

3.3.2. Reversible Inhibition

3.3.2. Clozapine Case 3: Reversible Inhibition

- Non-competitive:
  - The inhibitor binds to a different site than the substrate.
  - This does not appear to be important for psychiatrists.
- Competitive:
  - The inhibitor binds to the same site as the substrate.
  - Inhibition can be overcome by ↑ substrate C.
  - This is important for psychiatrists.
- As far as Dr. de Leon understands:
  - Caffeine is a dose-related competitive inhibitor of clozapine metabolism.
  - Sertraline may be a dose-related competitive inhibitor of clozapine metabolism in this case.

3.3.3. Summary for Psychiatrists

3.3.3. Clozapine Case 3: Inhibition Summary

- Due to limited studies:
  - Dr. de Leon focuses on the most important known issue: potency.
  - Competitive inhibition may be relevant, too.
- Three groups of inhibitors, according to potency:
  - Powerful inhibitors
  - Weak (or mild) to moderate inhibitors
  - On rare occasions, any drug can behave as an inhibitor due to:
    - saturation of the CYPs, and
    - competitive inhibition.

3.3.3. Inhibition: Summary for Clinicians

3.3.3.1. Powerful Inhibitors

3.3.3.2. Weak to Moderate Inhibitors

3.3.3.3. Any Drug Can, on Rare Occasions, Become an Inhibitor of the CYP involved in Its Own Metabolism

3.3.3.1. Powerful Inhibitors

3.3.3.1. Clozapine Case 3: Powerful Inhibitors

■ Some non-psychiatric drugs are powerful inhibitors.

Psychiatric drugs	Enzyme	Correction Factor
Antidepressants		
Fluvoxamine	CYP1A2/2C19	0.1-0.2 clozapine
	CYP1A2	0.3-0.5 olanzapine
Fluoxetine	CYP2D6/3A4	0.25
Paroxetine	CYP2D6	0.5
Mood Stabilizers		
Valproic Acid	CYP2C9	Irrelevant in psychiatry
	UGT1A4	0.5 lamotrigine

In his clinical practice, Dr. de Leon assumes that within therapeutic D ranges of inhibitor:

- D are not relevant and inhibition is maximal, and
- ↑ substrate D may not overcome inhibition.

3.3.3.2. Weak (or Mild) to Moderate Inhibitors

3.3.3.2. Clozapine Case 3: Weak/Moderate Inhibitors

Drug	CYP2C19	CYP2D6	CYP3A4
Antidepressants			
TCA tertiary[1]	Moderate	Weak	
Other TCAs		Weak	
Fluoxetine	Weak to moderate	Potent[2]	Weak to moderate
Fluvoxamine	Potent[2]	Weak	Moderate
Paroxetine	Weak	Potent[2]	Weak
Sertraline	Weak	Weak to moderate	Weak
Duloxetine		Moderate	
Bupropion		Moderate	
Antipsychotics			
Phenothiazines		Weak	
Asenapine		Weak	
Mood Stabilizers[3]			
Oxcarbazepine	Weak		

[1]Amitriptyline,clomipramine and imipramine are tertiary amines.

[2]Potent inhibition is included when drug causes weak to moderate inhibtion in other CYPs.

[3]Valproate appears to be a weak paliperidone inhibitor, but its mechanism is not well understood.

3.3.3.3. Any Drug, on Rare Occasions, Can Become an Inhibitor of the CYP Involved in Its Own

3.3.3.3. Any Drug Can Inhibit CYP Involved in Metabolism

- Any drug can inhibit CYP(s) involved in its own metabolism through competitive inhibition.
- On rare occasions this leads to clinically- relevant DDIs, usually in patients using polytherapy:
  - metabolism is compromised and
  - adding the drug may be the straw that breaks the camel's back.

3.4. SSRIs and Clozapine[5]

3.4. SSRIs and Clozapine

3.4.1. Facts to Remember

3.4.2. TDM Study

3.4.1. SSRIs and Clozapine: Facts to Remember

3.4.1 Clozapine Case 3: Remember about SSRIs

- DDI review http://www.ncbi.nlm.nih.gov/pubmed/24494611
  - Correction factor in the average clozapine patient:
    - Fluvoxamine: 0.1-0.2 (better to do TDM)
    - Fluoxetine & paroxetine: 0.75-0.80
  - Sertraline's inhibitory effects:
    - Weak to moderate: CYP2D6
    - Weak: other CYPs: (CYP1A2, CYP2C9, CYP2C19 & CYP3A4)
    - May be dose-related and not relevant unless in high doses

3.4.2. SSRIs and Clozapine: TDM Studies

3.4.2. SSRIs and Clozapine: TDM Studies

3.4.2.1. Italian Study: Correcting for Confounders

3.4.2.2. Old US Study

3.4.2.1. SSRIs and Clozapine: Italian TDM Study Controlling for Confounders

3.4.2.1. Clozapine Case 3: Italian TDM Study

Italian DDI study using intra-subject design and/or parallel design or patients studied for TDM http://www.ncbi.nlm.nih.gov/pubmed/18484549

	Correction Factor	95% CI
Phenobarbital	1.4	1.1-1.7
Smoking	1.2	1.1-1.4
Paroxetine	0.77	0.67-0.89
Fluoxetine	0.70	0.64-0.78
Fluvoxamine	0.28	0.22-0.35

3.4.2.1. Clozapine Case 3: Italian TDM Study

- Summary of Italian TDM study after correcting for other variables: http://www.ncbi.nlm.nih.gov/pubmed/18484549
  - Fluvoxamine had very powerful effects.
  - Fluoxetine and paroxetine had mild effects.
  - Citalopram had no significant effects.
  - Sertraline had no significant effects:
    - 8 patients on clozapine (200-400 mg/day)
    - 3 weeks of sertraline (50-100 mg/day)

    If sertraline's inhibitory effects are dose-related, a dose of 50-100 mg/day may not have been enough.

3.4.2.2. SSRIs and Clozapine: US TDM Study

3.3.4.2. Clozapine Case 3: US TDM Study

- An old US TDM study describes changes in total clozapine C associated with some SSRIs: http://www.ncbi.nlm.nih.gov/pubmed/8633698
  - Paroxetine had significant effects: ↑ 57% (N=16, mean dose 31 mg/day).
  - Fluoxetine had no significant effects: ↑ 30% (N=14, mean dose 39 mg/day).
  - Sertraline had no significant effects: ↑ 20% (N=10, mean dose 93 mg/day).

3.5. Sertraline-Clozapine DDI: Clinical Relevance

3.5. Clinical Relevance of Sertraline-Clozapine DDI

3.5.1. Clinical Relevance of This Case

3.5.2. Clinical Relevance in the Literature

3.5.3. Conclusion on Clinical Relevance

3.5.1. Sertraline-Clozapine DDI: Clinical Relevance of This Case

3.5.1. Clozapine Case 3: This Case's Clinical Relevance

- Our patient had a sertraline-clozapine DDI.
  - It had no clinical relevance and no symptoms of toxicity despite high Cs.
  - It had pharmacokinetic relevance. Sertraline discontinuation was associated with clinically relevant ↓ clozapine C.

3.5.1. Clozapine Case 3: This Case's Clinical Relevance

How do we estimate the pharmacokinetic relevance of this DDI?

3.5.1. Clozapine Case 3: This Case's Clinical Relevance

How do we estimate the pharmacokinetic relevance of this DDI?

By estimating the clozapine D change required to match it.

3.5.1. Clozapine Case 3: This Case's Clinical Relevance

- Clozapine C/D ratios:
  - No sertraline: clozapine C/D ratio = 1.25
  - On sertraline:
    - 300 mg/day: clozapine C/D ratio = 2.17
    - 150 mg/day: clozapine C/D ratio = 2.33

    Sertraline mean clozapine C/D ratio = 2.25
- Correction factor:

  $\frac{\text{clozapine C/D ratio - no sertraline}}{\text{clozapine C/D ratio - on sertraline}} = \frac{1.25}{2.25} = 0.56$

In summary, in this patient sertraline led to ↓ clozapine metabolism almost by half.

3.5.1. Clozapine Case 3: This Case's Clinical Relevance

- The effects of DDI vary from patient to patient. In this patient, sertraline 300 or 150 mg/day appears to be a clinically relevant inhibitor of clozapine metabolism.

3.5.2. Sertraline-Clozapine DDI: Clinical Relevance in the Literature

3.5.2. Clozapine Case 3: Clinical Relevance in the Literature

- The literature describes two cases with clinical relevance after adding sertraline to clozapine treatment:
  - ↑ OCD symptoms and ↑ clozapine C

    http://www.ncbi.nlm.nih.gov/pubmed/9004072
  - A seizure case: clozapine C not measured

    http://www.ncbi.nlm.nih.gov/pubmed/19617951

3.5.2. Sertraline-Clozapine DDI: Clinical Relevance in the Literature

3.5.2.1. Published Sertraline-Clozapine DDI: OCD Worsening

3.5.2.2. Published Sertraline-Clozapine DDI: Seizures

3.5.2.1. Published Sertraline-Clozapine DDI: OCD Worsening

http://www.ncbi.nlm.nih.gov/pubmed/9004072

3.5.2.1. Clozapine Case 3: OCD Worsening

- A 26-yo ♀ from Singapore (race not reported) with schizophrenia and compulsive behaviors (compulsive checking).
- Medications:
  - Clozapine D = 175 mg/day
  - Propranolol D = 10 mg/day and
  - Trihexyphenidyl D = 2 mg/day
- The addition of clozapine:
  - ↑ psychotic symptoms
  - ↑ compulsive checking and started rumination
- Clozapine C on 150 mg/day: 325 ng/ml

3.5.2.1. Clozapine Case 3: OCD Worsening

What was the baseline clozapine C/D ratio with a D=175 mg/day and C=325 ng/ml?

3.5.2.1. Clozapine Case 3: OCD Worsening

What was the baseline clozapine C/D ratio with a D=175 mg/day and C=325 ng/ml?

1.9 =(325/175).

3.5.2.1. Clozapine Case 3: OCD Worsening

Is this baseline clozapine C/D ratio=1.9 normal?

3.5.2.1. Clozapine Case 3: OCD Worsening

Is this baseline clozapine C/D ratio=1.9 normal?

Probably yes; the normal range is 1.2-2.4 in East Asians.

3.5.2.1. Clozapine Case 3: OCD Worsening

- 50 mg/day of sertraline were added:
  - worsening of OCD and psychosis
  - clozapine C = 695 ng/ml
    after 4 weeks on this sertraline D.

3.5.2.1. Clozapine Case 3: OCD Worsening

What was the clozapine C/D ratio on sertraline 50 mg/day with a D=175 mg/day and C=695 ng/ml?

3.5.2.1. Clozapine Case 3: OCD Worsening

What was the clozapine C/D ratio on sertraline 50 mg/day with a D=175 mg/day and C=695 ng/ml?

4.0=(695/175).

3.5.2.1. Clozapine Case 3: OCD Worsening

Is this clozapine C/D ratio=4.0 while on sertraline normal?

3.5.2.1. Clozapine Case 3: OCD Worsening

Is this clozapine C/D ratio=4.0 while on sertraline normal?

No, the normal range is 1.2-2.4 in East Asians.

3.5.2.1. Clozapine Case 3: OCD Worsening

- Discontinuing sertraline:
  - ↓ psychotic symptoms
  - 2 weeks later:

    ↓ clozapine C=460 ng/ml

3.5.2.1. Clozapine Case 3: OCD Worsening

What was the clozapine C/D ratio after sertraline discontinuation with a D=175 mg/day and C=460 ng/ml?

3.5.2.1. Clozapine Case 3: OCD Worsening

What was the clozapine C/D ratio after sertraline discontinuation with a D=175 mg/day and C=460 ng/ml?

2.6=(460/175).

3.5.2.1. Clozapine Case 3: OCD Worsening

Is this clozapine C/D ratio=2.6 after sertraline discontinuation normal?

3.5.2.1. Clozapine Case 3: OCD Worsening

Is this clozapine C/D ratio=2.6 after sertraline discontinuation normal?

Close to normal; the normal range is 1.2-2.4 in East Asians.

3.5.2.1. Clozapine Case 3: OCD Worsening

Sertraline	Clozapine		
	D	C	C/D ratio
mg/day	mg/day	ng/ml	
0	175	325	1.9
50 (4 weeks)	175	695	4.0
0 (2 weeks)	175	460	2.6

This appears to be an Asian ♀:

- with a low baseline clozapine metabolism, and
- a further dramatic ↓ clozapine metabolism after adding a low sertraline dose.

3.5.2.1. Clozapine Case 3: OCD Worsening

- OCD symptoms present in some schizophrenia patients.
- Case reports and small studies indicate adding clozapine can exacerbate OCD symptoms when OCD is pre-existing, or even start them. http://www.ncbi.nlm.nih.gov/pubmed/15885526
- Cases and small studies indicate clozapine can reduce OCD symptoms in schizophrenia patients. http://www.ncbi.nlm.nih.gov/pubmed/15048611
- There are no definitive studies and this is a complex area.

3.5.2.1. Clozapine Case 3: OCD Worsening

- In a recent review, Fonseka et al. described:

  http://www.ncbi.nlm.nih.gov/pubmed/25256097

  - In clozapine-treated patients:
    - 20-28% de novo OCD symptoms
    - 10-18% exacerbation of OCD symptoms
  - In olanzapine-treated patients:
    - 11-20% OCD symptoms (less well-studied)

3.5.2.2. Published Sertraline-Clozapine DDI: Seizures

http://www.ncbi.nlm.nih.gov/pubmed/19617951

3.5.2.2. Clozapine Case 3: Seizure

- 19-year-old Indian ♂ with schizophrenia
- Clozapine D = 300 mg/day
- Severe obsessive impulses of jumping from heights
- Sertraline was added:
  - started at D=50 mg/day
  - increased to D=100 mg/day after 4 days

3.5.2.2. Clozapine Case 3: Seizure

- One week after sertraline D was increased,
  - his mother reported deviation of mouth to the left and jerky facial movements;
  - in seconds he had a generalized tonic-clonic seizure.
- The patient reported his face twitching to the left:
  - starting on the day sertraline was added;
  - lasting a few seconds.
  - he had 7-8 episodes until the seizure generalized.

- Clozapine was switched to quetiapine.

3.5.2.2. Clozapine Case 3: Seizure

Is this a sertraline-clozapine DDI?

3.5.2.2. Clozapine Case 3: Seizure

Is this a sertraline-clozapine DDI?

Yes;
it looks like one.

3.5.2.2. Clozapine Case 3: Seizure

What are the pharmacological mechanisms behind this sertraline-clozapine DDI?

3.5.2.2. Clozapine Case 3: Seizure

What are the pharmacological mechanisms behind this sertraline-clozapine DDI?

They can be pharmacokinetic and/or pharmacodynamic.

3.5.2.2. Clozapine Case 3: Seizure

Is
a pharmacokinetic mechanism
possible?

3.5.2.2. Clozapine Case 3: Seizure

Is
a pharmacokinetic mechanism
possible?

Yes.

3.5.2.2. Clozapine Case 3: Seizure

- A pharmacokinetic DDI
  - cannot be ruled out,
  - but sertraline D was low (100 mg/day)
- In favor: clozapine-induced seizures may be dose-related.
  Avoid clozapine C >1000 ng/ml
- Measuring clozapine TDM is crucial for exploring the DDI pharmacokinetic component of adding sertraline.

3.5.2.2. Clozapine Case 3: Seizure

- Clozapine: ↓ seizure threshold; the worst among second-generation antipsychotics.
- A review of US company data:
  - Devinsky et al. (first 1418 patients):
    - prevalence: 2.8% http://www.ncbi.nlm.nih.gov/pubmed/2006003
    - accumulative risk: 10% after 3.8 years
    - dose-related: 4.4% in D ≥ 600 mg/day
      2.7% in D = 300-600 mg/day
      1% in D < 300 mg/day
  - Pacia & Devinsky (5629 patients, only 6 months):
    - prevalence:1.3% http://www.ncbi.nlm.nih.gov/pubmed/7991106
    - usually at high Ds ≥ 600 mg/day
    - if they happen at low Ds during the titration phase: history of seizures or epilepsy.

3.5.2.2. Clozapine Case 3: Seizure

Is a pharmacodynamic mechanism possible?

3.5.2.2. Clozapine Case 3: Seizure

Is a pharmacodynamic mechanism possible?

Yes.

3.5.2.1. Clozapine Case 3: Seizure

- A pharmacodynamic DDI is possible, too.
- Sertraline, as with other SSRIs, has a complex relationship with seizures:
  - Case reports have associated sertraline with seizures. http://www.ncbi.nlm.nih.gov/pubmed/10900533
  - An anticonvulsant effect is reported in:
    - an animal model http://www.ncbi.nlm.nih.gov/pubmed/23153716
    - pharmacoepidemiological studies, as SSRIs ↓ seizure risk vs. placebo
  - If partial seizures started the first day after adding sertraline, it suggests a pharmacodynamic component (too early for a relevant ↑ clozapine C).

3.5.3. Sertraline-Clozapine DDI: Conclusion on Clinical Relevance

3.5.2.3. Clozapine Case 3: Conclusion

Is it true that adding sertraline to clozapine may not cause a clinically-relevant DDI?

3.5.2.3. Clozapine Case 3: Conclusion

Is it true that adding sertraline to clozapine may not cause a clinically-relevant DDI?

Probably yes, in many cases.

3.5.2.3. Clozapine Case 3: Conclusion

Should you always expect that adding sertraline would not cause a clinically-relevant DDI with clozapine?

3.5.2.3. Clozapine Case 3: Conclusion

Should you always expect that
adding sertraline
would not cause
a clinically-relevant DDI
with clozapine?

No;
be careful with high doses.

Questions

- Please review the 10 questions in the pdf file entitled “Questions on the Presentation: Clozapine Case 3”.
- You will find the answers on the last slide after the “Thank you slide”. No peeking until you have answered all the questions.
- If you do not answer all the questions correctly, please review the PowerPoint presentation again to reinforce the pharmacological concepts.

Thank you

Answers

1. B
2. C
3. B
4. B
5. D
6. B
7. A
8. A
9. A
10. A