Clozapine Case 6: Half-Life 1-16-16

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6. Clozapine Case 6

J Clin Psychopharmacol 1996;16:193-4.

http://www.ncbi.nlm.nih.gov/pubmed/8690839

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 half-life is important for understanding clozapine:
   - 2.1. Therapeutic drug monitoring
   - 2.2. Dosing
3. Summarize how unusual half-lives influence the prescription of some psychiatric drugs.

Warnings

- As Dr. de Leon has no formal training in pharmacology, it is possible that in the process of explaining the concepts of half-life to make them understandable to clinicians such that they can applied to clinical practice, he has oversimplified too much. To combat this problem, he provides references in pharmacological textbooks and articles that can be checked by readers.

Abbreviations

- AP: antipsychotic
- C: concentration
- CYP: cytochrome P450
- D: dose
- DDI: drug-drug intercatione
- TDM: therapeutic drug monitoring

Clozapine Case 6

6.1. Case

6.2. Additional Case

6.3. Clozapine Half-Life
6.4. Half-Life and TDM
6.5. Half-Life and Dosing
6.6. Half-Life Concept in the Pharmacology Literature
6.7. Clinical Applications of Half-Life

Clozapine Case 6

6.1. Case

6.1. Case 6: Introduction

6.1.1. Description

6.1.2. Questions

6.1.3. Data

6.1.1. Case Description

6.0.1. Clozapine Case 6: Description

- A 34-year-old Caucasian ♂ with chronic undifferentiated schizophrenia.
- First TDM:
  - Clozapine D = 900 mg/day
  - Clozapine C = 485 ng/ml
  - Norclozapine C = 298 ng/ml
  - Total Clozapine C = 783 ng/ml
- 1 week after stopping clozapine:
  - Clozapine C = 18 ng/ml
  - Norclozapine C = 14 ng/ml
  - Total Clozapine C = 32 ng/ml
- 2 week after stopping clozapine:
  - Clozapine & Norclozapine Cs: undetectable

6.1.2. Case Questions

6.1.2. Clozapine Case 6: Questions

What is the pharmacological concept that explains how clozapine Cs ↓ after stopping clozapine?

6.1.2. Clozapine Case 6: Questions

What is the pharmacological concept that explains how clozapine Cs ↓ after stopping clozapine?

Half-life.

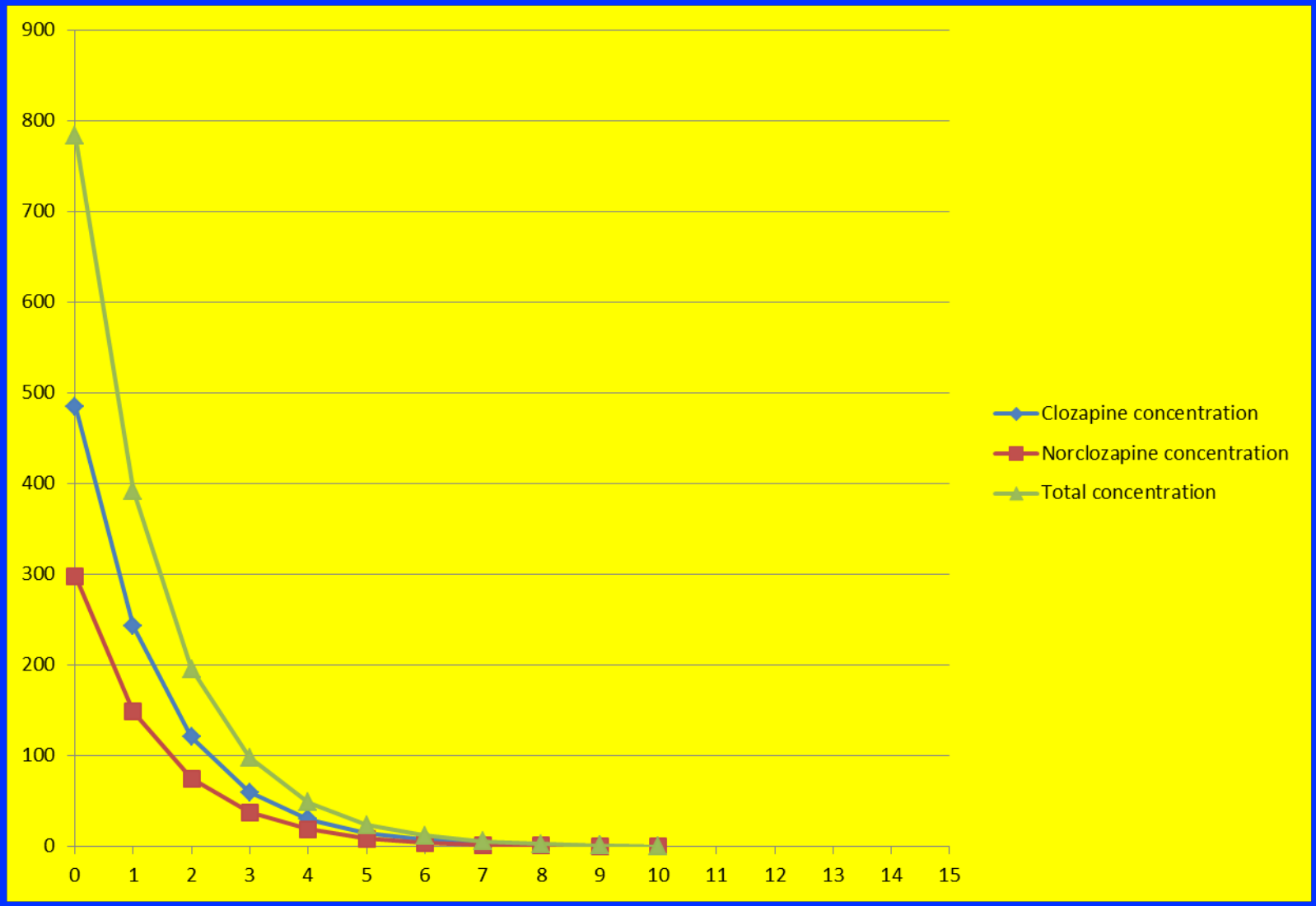
6.1.2. Clozapine Case 6: Questions

How do you define half-life?

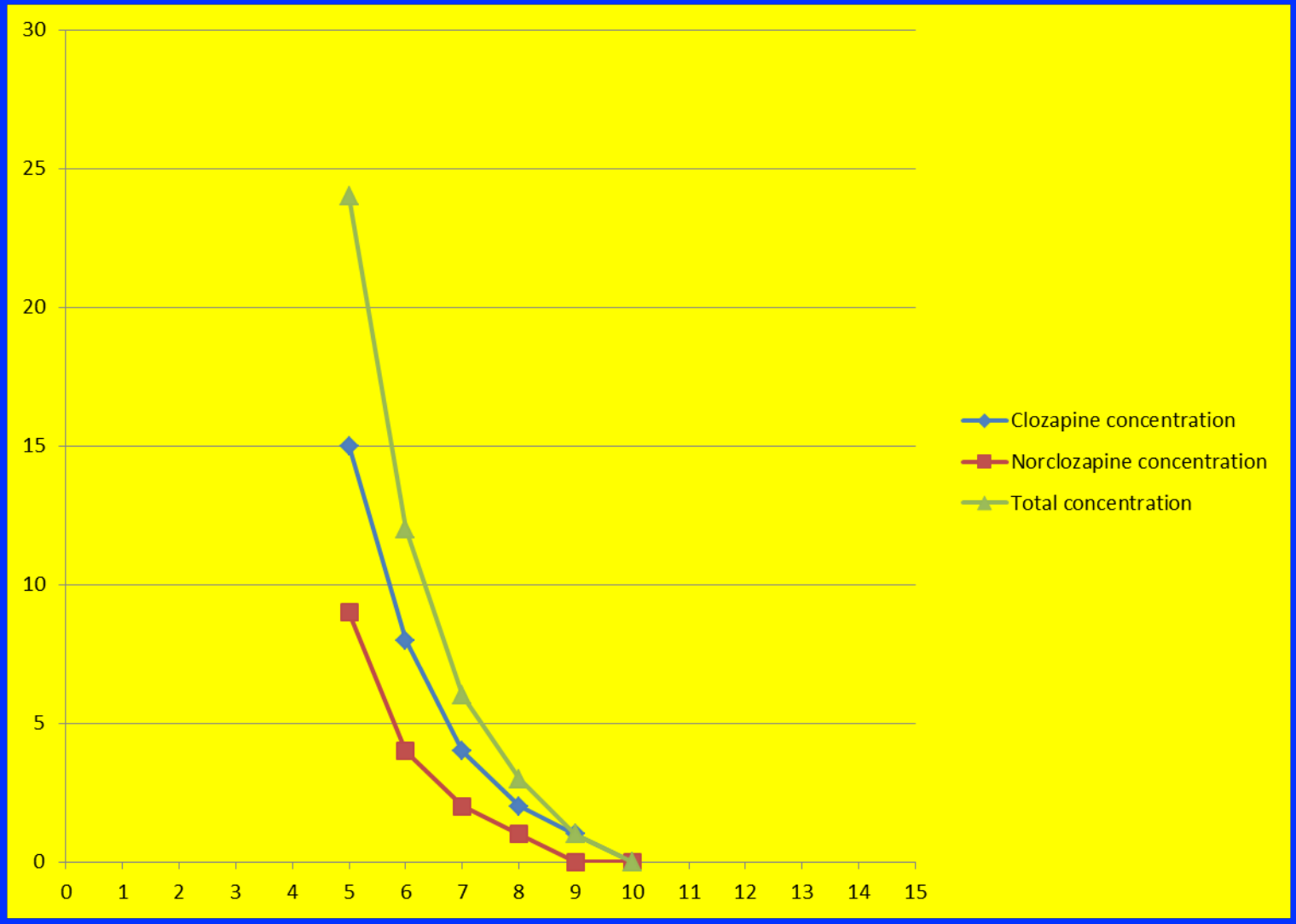
6.1.2. Clozapine Case 6: Questions

- Half-life: time to ↓ serum C to ½.
  2 half-lives:↓ serum C to ½ of ½ (¼).
  The serum C decline in time in an exponential manner (a plot of the logarithm of serum C vs. the elapsed time is a straight line).
- To make the representation easier in this patient, imagine that the half-lives of clozapine and norclozapine are 24 hours (1 day).

6.1.2. Clozapine Case 6: Half-lives=24 hours



6.1.2. Clozapine Case 6: Same Graphic Focus on > 5 Half-lives by Zooming in the Last Part of Prior Curve

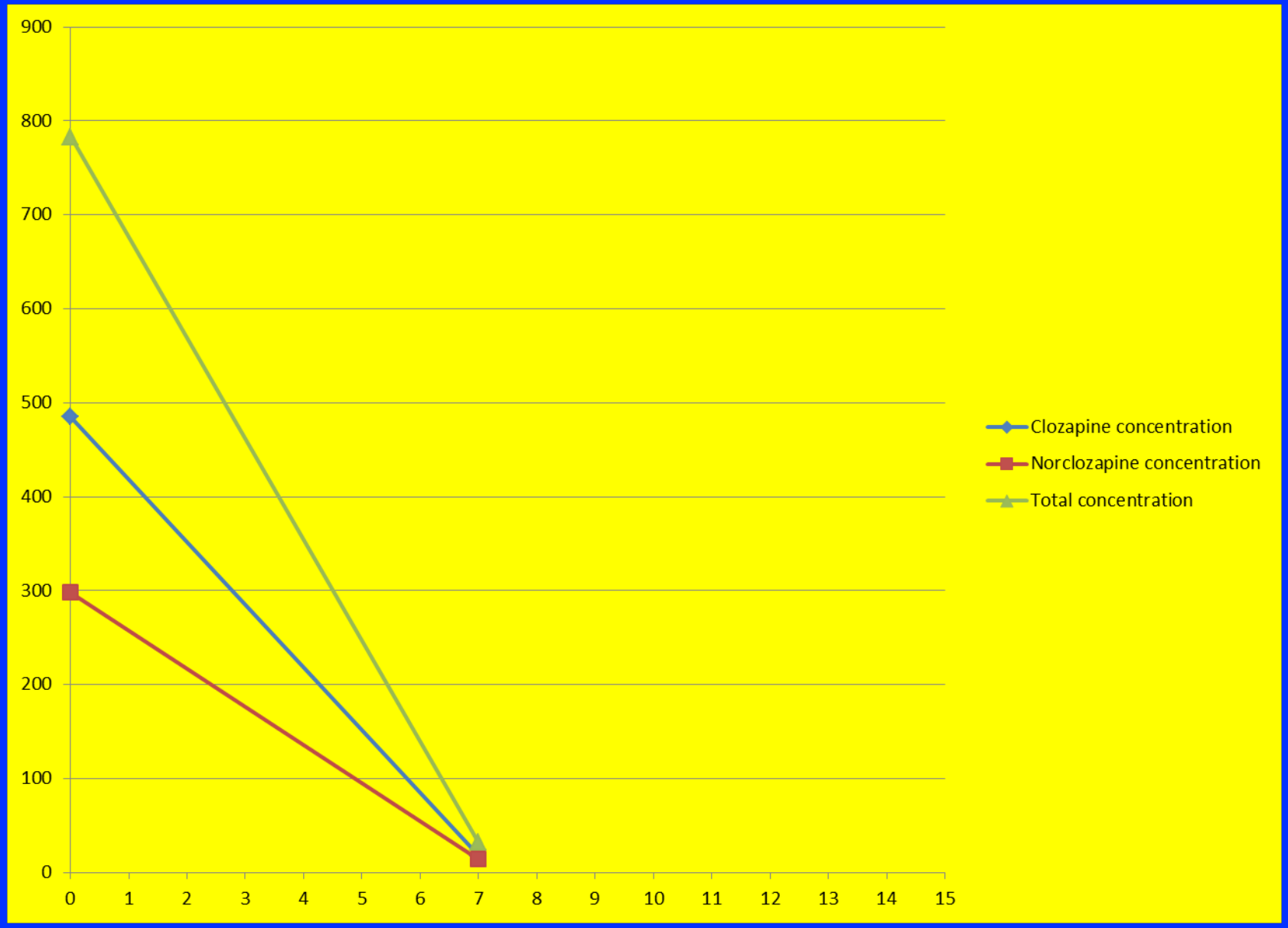


6.1.2. Clozapine Case 6: Questions

- After 5 half-lives: serum C is almost completely eliminated.
- As a matter of fact, using an exponential curve:
  - After 5 half-lives: 95% eliminated
  - After 7 half-lives: 99% eliminated

6.1.3. Case Data

6.1.3. Clozapine Case 6: Case Data



6.1.3. Clozapine Case 6: Data

- If we focus on clozapine C:
  - Day 0: Clozapine C = 485 ng/ml
  - Day 7: Clozapine C = 18 ng/ml
    Only 3.7% left (18/485)
    or 96.3 % eliminated (485-18/485)
- If we focus on total clozapine C:
  - Day 0: Total clozapine C = 783 ng/ml
  - Day 7: Clozapine C = 32 ng/ml
    Only 4.1% left (32/783)
    or 95.9 % eliminated (485-18/485)

6.1.3. Clozapine Case 6: Data

- In 7 days a little more than 95% was eliminated.
- To simplify, let's assume that is close enough to 95% which corresponds to 5 half-lives.

  7 days = 168 hours

  Therefore this provides a clozapine half-life = 34 hours (168/5)

  in this patient.
- A rough estimation: 2 data points

6.2. Additional Case

6.2. Case 6: Additional Case

6.2.1. Description

6.2.2. Calculation

6.2.1. Additional Case: Description

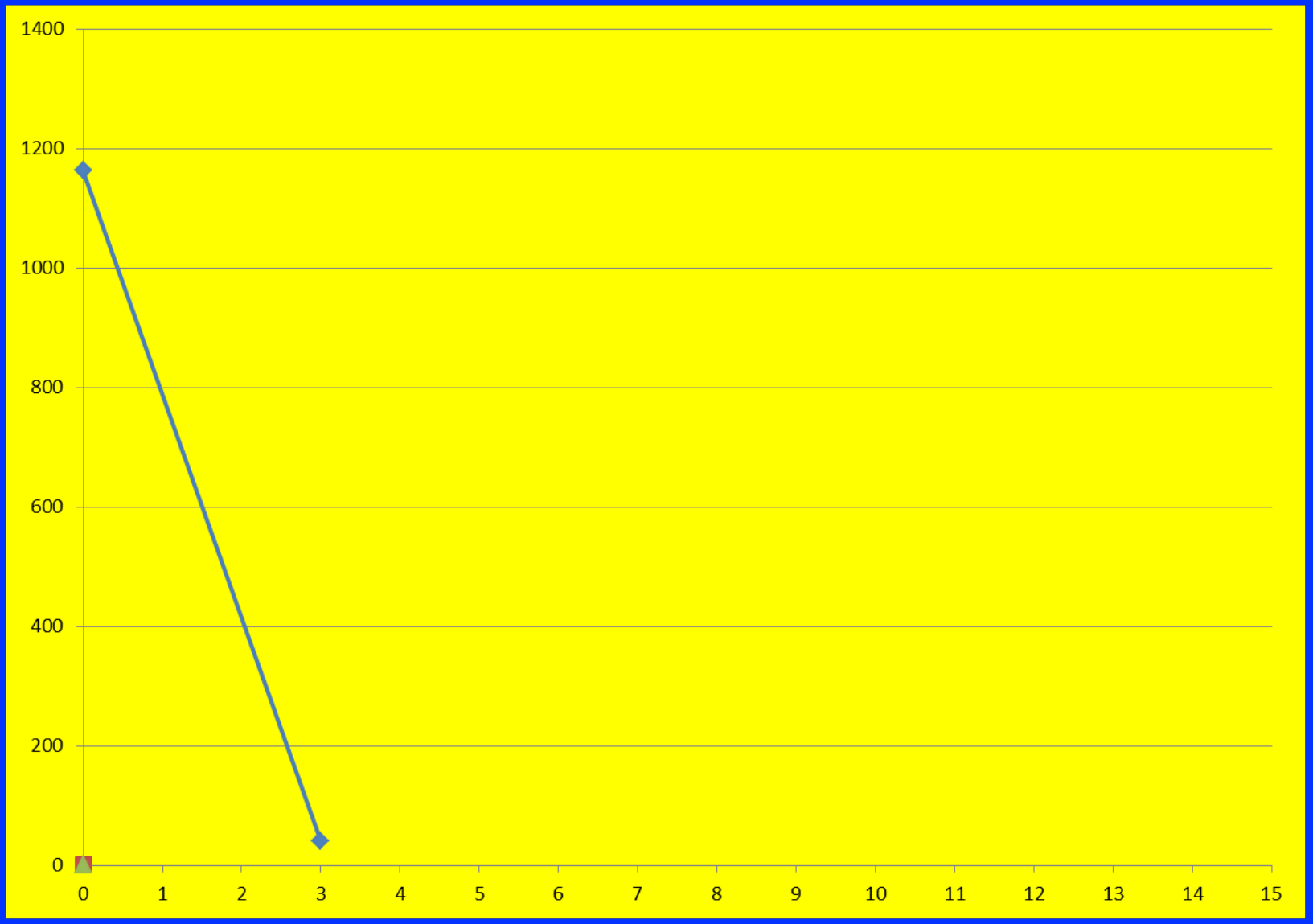
6.2.1. Additional Case: Description

- A 37-year-old Caucasian ♂ with schizophrenia.
- First TDM early Friday morning:
  - Clozapine D = 250 mg/day at night
  - Clozapine C = 1163 ng/ml
  - Norclozapine C not measured

  Laboratory called C “toxic” on Friday evening. Clozapine was stopped (no toxicity signs).
- 3 days after stopping (early Monday morning):
  - Clozapine C = 41 ng/ml

  The last dose was Thursday night or approximately 84 hours before.

6.2.1. Additional Case: Description



6.2.2. Additional Case: Calculation

6.2.2. Additional Case: Calculation

- Calculations for clozapine C:
  - Day 0: clozapine C = 1163 ng/ml
  - Day 3: clozapine C = 41 ng/ml

    Only 3.5% left (41/1163)

    or 96.5% eliminated (1163-41/1163).
- Let's assume that is close enough to 95% which corresponds to 5 half-lives.

  Discontinuation has lasted 84 hours

  Therefore this provides a clozapine half-life = 17 hours (84/5) in this patient.

6.3. Clozapine Half-Life

6.3. Clozapine Case 6: Clozapine Half-Life

- Clozapine half-life rough estimations only using 2 data points:
  - first case = 34 hours
  - additional case = 17 hours

6.3. Clozapine Case 6: Clozapine Half-Life

What is
clozapine half-life,
according to
US prescribing information?

6.3. Clozapine Case 6: Clozapine Half-Life

What is
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according to
US prescribing information?

12 hours (range 4-66).

http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5f0c6f5f-b906-4c8f-8580-3939a476a1c1

6.3. Clozapine Case 6: Clozapine Half-Life

- 2 patients suggest that in the clinical environment, half-life is clearly > 12 hours.
- Moreover, the range provided by clozapine prescribing information, 4-66 hours is too wide to be helpful to clinicians.
- A review of clozapine half-life describes how measuring Cs for longer times provides longer half-lives of up to 29 hours. Clozapine may deposit in fat tissue; this ↑ its half-life. http://www.ncbi.nlm.nih.gov/pubmed/24934547

6.4. Half-Life and TDM

6.4. Clozapine Case 6: Half-Life and TDM

- There is general agreement that the concept of half-life is important in TDM, in order to measure Cs at steady-state. Most textbooks and articles assume an exponential curve to calculate it. Bauer's textbook explains:
  - 5 half-lives: 95% of steady state Cs, and
  - 7 half-lives: 99% of steady state Cs.

http://www.amazon.com/Clinical-Pharmacokinetics-Handbook-Larry-Bauer/dp/007142542X/ref=sr_1_sc_3?s=books&ie=UTF8&qid=1452114772&sr=1-3-spell&keywords=bauer+clinical+pharmacokinetcis

6.4. Clozapine Case 6: Half-Life and TDM

What do you mean by steady-state Cs?

6.4. Clozapine Case 6: Half-Life and TDM

- Steady-state serum (or plasma) Cs:
  - occur when equilibrium is reached, equilibrium between input and output (between absorption and elimination)
- You need wait until steady-state has been reached to interpret TDM correctly. Moreover, you need use trough Cs. Trough Cs are the lowest Cs of the day, in the early morning before any medication is given.

6.5. Half-Life and Dosing

6.5. Clozapine Case 6: Half-Life and Dosing

- Half-life is very important for dosing.
- Rowland & Tozer's textbook describes dosing for drugs with half-lives:
  - >24 hours: administered once a day.
  - 8-24 hours: administered every half-life. This means half-life is around:
    - 12 hours: administer twice a day.
    - 8 hours: administer three times a day.

http://www.amazon.com/Clinical-Pharmacokinetics-Pharmacodynamics-Concepts-Applications/dp/0781750091/ref=sr_1_1?s=books&ie=UTF8&qid=1452116150&sr=1-1&keywords=rowland+pharmacokinetics

6.6. Half-Life Concept in the Pharmacological Literature

6.6. Clozapine Case 6: Half-Life & Pharmacological Literature

- Textbooks/articles by pharmacologists on half-life tend to be very complex and not easy to understand for clinicians.
- To start, there are multiple types of half-lives.
- The half-life described after stopping a drug is usually called:
  - elimination half-life http://www.ncbi.nlm.nih.gov/pubmed/21499748

    or
  - terminal half-life http://www.ncbi.nlm.nih.gov/pubmed/11368290
- Half-life calculated using single-dosing does not represent half-life under repeated dosing very well.

6.6. Clozapine Case 6: Half-Life & Pharmacological Literature

- Wright & Body http://www.ncbi.nlm.nih.gov/pubmed/11368290 on the concept of half-life:
  - It assumes an exponential elimination.

    (Wright & Body state, "The use of a half-life implies a linear, first-order, time-invariant system.")
  - It is a good approximation for:
    - dosing
    - time-course Cs: approach to steady-state and washout after discontinuation
  - It is impractical for individualization.

6.6. Clozapine Case 6: Half-Life & Pharmacological Literature

- Most pharmacology textbooks describe drug half-life as influenced by:
  - the clearance (or elimination), and
  - the volume of distribution

    Drugs can be distributed in different tissues.
- If a drug can be stored in the fat tissue, elimination may be slow once the drug is stopped. Elimination is first from blood, then from fat.

  Haloperidol Cs can remain detectable weeks after discontinuation of the oral formulation.

  http://www.ncbi.nlm.nih.gov/pubmed/15538130

6.6. Clozapine Case 6: Half-Life & Pharmacological Literature

- Volume of distribution for drugs:
  - textbooks describe a 2-compartment model:
    - a central (blood, liver and kidney), and
    - a peripheral: more slow equilibrium (muscle and fat)

http://www.amazon.com/Clinical-Pharmacokinetics-Pharmacodynamics-Concepts-Applications/dp/0781750091/ref=sr_1_1?s=books&ie=UTF8&qid=1452116150&sr=1-1&keywords=rowland+pharmacokinetics

  - some drugs fit a 3-compartment model by having two peripheral compartments:
    - a shallow peripheral compartment, and
    - a deep peripheral compartment: fat tissue with very slow deposit and slow release

http://www.ncbi.nlm.nih.gov/pubmed/1101062

6.6. Clozapine Case 6: Half-Life & Pharmacological Literature

- Some antipsychotics may deposit in fat (the deep peripheral compartment), including:
  - phenothiazines (drug family of chlorpromazine) http://www.ncbi.nlm.nih.gov/pubmed/2371373
  - haloperidol: http://www.ncbi.nlm.nih.gov/pubmed/15538130
  - clozapine: http://www.ncbi.nlm.nih.gov/pubmed/24934547

  This increase their elimination half-life.

6.7. Clinical Applications of Half-Life

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6.7.1. Estimating Half-Lives

6.7.2. Average Half-Lives May Not Represent Your Patient

6.7.3. Second-Generation AP Half-Lives

6.7.4. Unusual Situations to Remember: Half-Life of Endogenous Targets

6.7.1. Estimating Half-Lives

6.7.1. Clozapine Case 6: Estimating Half-Lives

- Dr. de Leon uses, as a mnemonic rule, the number of typical administrations per day:
  - once a day: half-life of at least 24 hours
  - twice a day: half-life around 12 hours
  - three times a day: half-life around 8 hours
- This helps him to remember rules of TDM after dose changes. If drugs are typically administered:
  - once a day: wait 5 days, or better 1 week
    trough Cs are a good measure for TDM
  - twice a day: wait 3 days after major C
    major C fluctuations during the day

The hour of last dose may influence trough Cs.

6.7.2. Average Half-Lives May Not Represent Your Patient

6.7.2. Clozapine Case 6: Average Half-Life May not Represent Your Patient

- If your patient has an unusual:
  - genetic profile,
  - environmental profile, or
  - personal profile,

  he/she may not be well-represented by mean half-life.
- For example, lamotrigine half-life in adults (prescribing information): http://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=LAMOTRIGINE

	Lamotrigine half-life
Co-medication	Mean (range)
Inducers	12.6 (7.5-23.1) hours
No other meds	25.4 (11.6-61.6) hours
Inducers + valproate	27.2 (11.2-51.6) hours
Valproate	70.3 (41.9-113.5) hours

6.7.3. Second-Generation AP Half-Lives

6.7.3. Second-Generation AP Half-Lives

6.7.3.1. Available Data

6.7.3.2. Poorly Understood

6.7.3.1. Second-Generation AP with Available Data on Half-Lives

6.7.3.1. Clozapine Case 6: APs with Available Data on Half-Lives

- Administered twice a day: half-lives <12 hours
  - asenapine
  - iloperidone
  - quetiapine (2 or 3 times a day)
  - ziprasidone
- Can be administered once a day: half-life around 24 hours
  - amisulpride
  - clozapine
  - lurasidone
  - olanzapine
  - paliperidone
  - risperidone (9-hydroxyrisperidone has long half-life)

6.7.3.1. Clozapine Case 6: APs with Available Data on Half-Lives

- Aripiprazole has a very long half-life.
  - Prescribing information:

http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c040bd1d-45b7-49f2-93ea-aed7220b30ac

    - half-life is about 75 hours (3.1 days).
    - half life of the metabolite is about 94 hours (3.9 days).
    - "Steady-state concentrations are attained within 14 days of dosing for both active moieties."
  - Dr. de Leon:
    - is not sure of the metabolite's clinical relevance.
    - summarizes by saying that reaching steady-state takes > 2 weeks

6.7.3.1. Clozapine Case 6: APs with Available Data on Half-Lives

- Brexpiprazole has a very long half-life.
  - Prescribing information:

    http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2d301358-6291-4ec1-bd87-37b4ad9bd850
    - its half-life is 91 hours (3.8 days).
  - Dr. de Leon:
    - summarizes it by saying that reaching steady-state takes > 2 weeks.

6.7.3.1. Clozapine Case 6: APs with Available Data on Half-Lives

- Cariprazine has an extremely long half-life.
  - Prescribing information:

http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4b5f7c65-aa2d-452a-b3db-bc85c06ff12f

    - half-life: cariprazine: 2-4 days
      active metabolite: 1-3 weeks
      (didesmethyl-cariprazine)
    - "The time to reach steady state for the major active metabolite DDCAR was variable across patients, with some patients not achieving steady state at the end of the 12 week treatment."

  - Dr. de Leon has no clinical experience:
    Steady state takes months (unclear how many).
    - 2.5 – 4 months: metabolite half-life of 2-3 weeks;
      see article http://www.ncbi.nlm.nih.gov/pubmed/23966785
    - 1.4 – 4 months: metabolite half-life of 1-3 weeks;
      see prescribing information

6.7.3.2. Poorly Understood Second-Generation AP Half-Lives

6.7.3.2. Clozapine Case 6: Poorly Understood AP Half-Lives

- Quetiapine extended-release tablet:
  - designed to be administered once a day by a mechanism that slowly releases quetiapine
  - unclear how to translate that to a half-life
  - be sure that you do not interfere absorption; do not administer with food.

6.7.3.2. Clozapine Case 6: Poorly Understood AP Half-Lives

- Long-acting aripiprazole half-life:
  - prescribing information:

http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ee49f3b1-1650-47ff-9fb1-ea53fe0b92b6

"After gluteal administration, the mean apparent aripiprazole terminal elimination half-life was 29.9 days and 46.5 days after multiple injections for every 4-week injection of ABILIFY MAINTENA 300 mg and 400 mg, respectively. Steady state concentrations for the typical subject were attained by the fourth dose for both sites of administration.."

- Dr. de Leon's summary:
  - issue is not well-studied
  - be very careful when prescribing long-acting aripiprazole
  - consider TDM after 4 doses in unusual situations (e.g. DDIs)

6.7.3.2. Clozapine Case 6: Poorly Understood AP Half-Lives

- Paliperidone palmitate half-life:
  - Prescribing information: 25-49 days

http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1af14e42-951d-414d-8564-5d5fce138554

> "The median apparent half-life of paliperidone following INVEGA SUSTENNA® single-dose administration over the dose range of 39 mg – 234 mg ranged from 25 days – 49 days."

  - Dr. de Leon:
    - issue is not well-studied
    - be very careful when prescribing long-acting paliperidone
    - consider TDM after 4 injections in unusual situations (e.g. DDI)

6.7.3.2. Clozapine Case 6: Poorly Understood AP Half-Lives

- Risperidone injection half-life:
  - Prescribing information
    - ” Steady-state plasma concentrations are reached after 4 injections and are maintained for 4 to 6 weeks after the last injection.”
    - “The apparent half-life of risperidone plus 9-hydroxyrisperidone following RISPERDAL CONSTA® administration is 3 to 6 days, and is associated with a monoexponential decline in plasma concentrations. This half-life of 3–6 days is related to the erosion of the microspheres and subsequent absorption of risperidone. The clearance of risperidone and risperidone plus 9-hydroxyrisperidone was 13.7 L/h and 5.0 L/h in extensive CYP 2D6 metabolizers, and 3.3 L/h and 3.2 L/h in poor CYP 2D6 metabolizers, respectively. No accumulation of risperidone was observed during long-term use (up to 12 months) in patients treated every 2 weeks with 25 mg or 50 mg RISPERDAL CONSTA®. The elimination phase is complete approximately 7 to 8 weeks after the last injection.”

http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=bb34ee82-d2c2-43b8-ba21-2825c0954691

6.7.3.2. Clozapine Case 6: Poorly Understood AP Half-Lives

- Practical issues in prescribing long-acting risperidone injections:
  - Dr. de Leon has seen several patients with:
    - too low Cs on long-acting risperidone, and
    - good Cs on oral risperidone

    Some were obese patients.

    He has commented on the issue in a published review: http://www.ncbi.nlm.nih.gov/pubmed/20118446

"The first author's experience and some preliminary reports by others[31] suggest a few subjects that have detectable levels with oral R may have undetectable concentrations with long-acting injections. More experience is needed to provide recommendations on how to interpret levels in patients taking long-acting R."

6.7.3.2. Clozapine Case 6: Poorly Understood AP Half-Lives

- Practical recommendations for prescribing long-acting risperidone injection:
  - The release system of this drug formulation appears extremely complex to Dr. de Leon.
  - TDM studies of patients on long-acting risperidone are desperately needed.
  - Be very careful when prescribing long-acting risperidone.
  - Consider TDM in all patients after four injections.

6.7.4. Unusual Situations to Remember: Half-Life of Endogenous Targets

6.7.4. Clozapine Case 6: Unusual Situations Regarding Half-Lives

- Until now, it has been assumed that its presence in serum is what determines the duration of the effects of a drug.
- Aspirin is a peculiar drug:
  - eliminated within 2 hours
  - irreversible inhibition of prostaglandin cyclooxygenase which lasts for several days.

6.7.4. Clozapine Case 6: Unusual Situations Regarding Half-Lives

Can you think of any pharmacological action of a psychiatric drug that is influenced by factors other than the drug's half-life?

6.7.4. Clozapine Case 6: Unusual Situations Regarding Half-Lives

Can you think of any pharmacological action of a psychiatric drug that is influenced by factors other than the drug's half-life?

Yes, the action of inducers.

6.7.4. Clozapine Case 6: Unusual Situations Regarding Half-Lives

- See the presentation
  "Induction by Antiepileptic Drugs: An Update for Clinicians".
- Inducers:
  - Their maximum effects take time.
  - Once discontinued there is a delay, until the excess enzyme is destroyed.
    - the half-life of the enzyme is what is important.
    - different metabolic enzymes have different half-lives.

6.7.4. Clozapine Case 6: Unusual Situations Regarding Half-Lives

- See the presentation “Clozapine Case 3: Sertraline”.
  - Irreversible inhibitors:
    - Mechanism-based inhibition is a type of inhibition that destroys the enzyme. It requires the synthesis of a new one.
    - Paroxetine and possibly fluoxetine may cause this type of CYP inhibition.
    - The clinical relevance of mechanism-based inhibition is unclear to Dr. de Leon.
- See the presentation “Antidepressant Pharmacokinetics”.
  - Norfluoxetine has a very long half-life.
    Steady state usually requires 2-3 months
    and may take up to 6 months.
    Complete elimination from body also takes 2-3 months
    (up to 6 months in some patients) after discontinuation.

Questions

- Please review the 10 questions in the pdf document entitled “Questions on the Presentation: Clozapine Case 6 Half Life”.
- 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. D
2. D
3. A
4. A
5. D
6. A
7. D
8. B
9. D
10. B