Quetiapine Case 1
Warfarin
1-23-16

Jose de Leon, MD

1. Quetiapine Case 1

J Clin Psychopharm 1999;19:382-3

http://www.ncbi.nlm.nih.gov/pubmed/10440472

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 quetiapine safety, one must consider:
    - 2.1. Personal, environmental and genetic factors.
    - 2.2. Pharmacodynamics and pharmacokinetics.
3. Be familiar with warfarin and phenytoin pharmacology.

Abbreviations

- ADR: adverse drug reaction
- AED: anti-epileptic drug
- C: concentration
- D: dose
- DDI: drug-drug interaction
- INR: international normalized ratio
- PM: poor metabolizer. They lack active CYP.
  For CYP2D6 and CYP2C19, PMs exist.
  For CYP2C9, PMs do not exist, but
  some individuals have very low activity.
- TDM: therapeutic drug monitoring
- UM: ultrarapid metabolizer

Quetiapine Case 1

1.0. Case Description
1.1. Phenytoin Pharmacology

1.2. Warfarin Pharmacology

1.3. Olanzapine Pharmacology

1.4. Quetiapine Pharmacology

1.5. Phenytoin's Role in This Case
1.6. Relevance of This Case Report

Quetiapine Case 1

1.0. Case Description

1.1. Phenytoin Pharmacology

- 1.1.1. Pharmacokinetics
- 1.1.2. Pharmacodynamics

1.2. Warfarin Pharmacology

- 1.2.1. Pharmacodynamics
- 1.2.2. Pharmacokinetics

1.3. Olanzapine Pharmacology

- 1.3.1. Pharmacokinetics
- 1.3.2. Pharmacodynamics

1.4. Quetiapine Pharmacology

- 1.4.1. Pharmacokinetics
- 1.4.2. Pharmacodynamics
- 1.4.3. Quetiapine DI in This Case

1.5. Phenytoin's Role in This Case

1.6. Relevance of This Case Report

- 1.6.1. Initial Recommendation at Time of Publication (1999)
- 1.6.2. PubMed Search
- 1.6.3. Review of Articles
- 1.6.4. Generalization from a Case Report

1.0. Quetiapine Case 1: Case Description

1.0. Quetiapine Case 1: Introduction

- 71-year-old Caucasian ♀
- Diagnosis of vascular dementia
- Medications:
  - phenytoin for seizures
  - warfarin for deep vein thrombosis
- Target INR values for this patient:
  2.0 – 3.0

1.1. Phenytoin Pharmacology

1.1. Quetiapine Case 1: Phenytoin

What do you know about phenytoin pharmacology?

1.1. Phenytoin Pharmacology

1.1.1. Phenytoin Pharmacokinetics

1.1.2. Phenytoin Pharmacodynamics

1.1.1. Phenytoin Pharmacokinetics

1.1.1. Quetiapine Case 1: Phenytoin Pharmacokinetics

What do you know about phenytoin pharmacokinetics?

1.1.1. Quetiapine Case 1: Phenytoin Pharmacokinetics

- Very complex pharmacokinetics:
  - complex metabolism
  - narrow therapeutic window
  - non-linear kinetics
    particularly during intoxication
  - complex DDIs

1.1.1. Phenytoin Pharmacokinetics

1.1.1.1. Metabolism
1.1.1.2. Therapeutic Window
1.1.1.3. Non-Linear Kinetics
1.1.1.4. DDIs

1.1.1.1. Phenytoin Metabolism

1.1.1.1. Quetiapine Case 1: Phenytoin Metabolism

- Phenytoin metabolism:
  - Main enzyme is: CYP2C9

    Second enzyme: CYP2C19

http://www.ncbi.nlm.nih.gov/pubmed/15557548

  - Others: CYP2C18 and CYP3A4

1.1.1.1. Quetiapine Case 1: Phenytoin Metabolism

Is CYP2C9 polymorphic?

1.1.1.1. Quetiapine Case 1: Phenytoin Metabolism

Is CYP2C9 polymorphic?

Yes.

1.1.1.1. Quetiapine Case 1: Phenytoin Metabolism

- CYP2C9 alleles: http://www.ncbi.nlm.nih.gov/pubmed/15637526
  - *2: minor ↓ in activity
    11% of Caucasians
    (lower % in other races)
  - *3: moderate ↓ in activity
    7% of Caucasians
    (lower % in other races)

1.1.1.1. Quetiapine Case 1: Phenytoin Metabolism

- CYP2C9 polymorphism:

Alleles	Activity	(up to 1.0)
*1/*1	Normal	(1.00)
*1/*2	Minor ↓	(0.82)
*2/*2	Moderate ↓	(0.70)
*1/*3	Moderate ↓	(0.56)
*2/*3	Moderate ↓	(0.39)
*3/*3	Very low	(0.13)

It varies from drug to drug. The correction factor for phenytoin on CYP2C9 *3/*3 is 0.65.

http://www.ncbi.nlm.nih.gov/pubmed/23344982

1.1.1. Quetiapine Case 1: Phenytoin Metabolism

Is CYP2C19 polymorphic?

1.1.1. Quetiapine Case 1: Phenytoin Metabolism

Is CYP2C19 polymorphic?

Yes.

1.1.1.1. Quetiapine Case 1: Phenytoin Metabolism

- CYP2C19 PMs:
  - East Asians: 25 %
  - Other races: <5%

- CYP2C19 UMs:

  *17: associated with ↑ expression

  Its clinical relevance is not well established.
  - The frequency is 1-5% for *17/*17.
  - The frequency is higher with only one *17.

See the presentation “Pharmacogenetic Tests in Psychiatry” for more details.

1.1.1.2. Phenytoin Therapeutic Window

1.1.1.2. Quetiapine Case 1:

Phenytoin Therapeutic Window

What do you know about phenytoin TDM?

1.1.1.2. Quetiapine Case 1: Phenytoin Therapeutic Window

- Typical therapeutic range:
  10-20 mcg/mL (mg/L)
- This is a narrow therapeutic index (or window).
  If you divide 20/10=2.
  This is <3 and indicates a narrow therapeutic window.

For more details on therapeutic index, see the TDM section on the presentation “Pharmacokinetics of Oral Second-Generation Antipsychotics.”

1.1.1.2. Quetiapine Case 1: Phenytoin Therapeutic Window

Should you worry about phenytoin intoxications?

1.1.1.2. Quetiapine Case 1: Phenytoin Therapeutic Window

Should you worry about phenytoin intoxications?

Yes, very much.

1.1.1.2. Quetiapine Case 1: Phenytoin Therapeutic Window

Why do you need to worry so much?

1.1.1.2. Quetiapine Case 1: Phenytoin Therapeutic Window

Why do you need to worry so much?

Phenytoin follows non-linear kinetics during intoxications.

1.1.1.3. Non-Linear Kinetics

1.1.1.3. Quetiapine Case 1: Phenytoin Kinetics

- Phenytoin's non-linear kinetics is:
  - dose-dependent, and
  - capacity-limited.
- Dose-dependent kinetics: changes with dose, (more precisely is concentration-dependent).
- Capacity-limited: metabolism can easily reach saturation when you are close to the upper therapeutic range (20 mcg/ml).

1.1.1.3. Quetiapine Case 1: Phenytoin Kinetics

What is the clinical relevance of this?

1.1.1.3. Quetiapine Case 1: Phenytoin Kinetics

What is the clinical relevance of this?

Be careful with high serum Cs.

1.1.1.3. Quetiapine Case 1: Phenytoin Kinetics

- With Cs around 20 mcg/mL, the CYPs (CYP2C9 and CYP2C19) can be saturated.
- Extraordinarily long phenytoin half-lives have been described during Intoxication.
- This requires the complete discontinuation of phenytoin for ≥ 2-3 days until Cs < 20 mcg/ml and metabolism normalizes.

1.1.1.3. Quetiapine Case 1: Phenytoin Kinetics

- Non-linear kinetics should be considered for dosing. ↑ dose slowly to reach therapeutic C.

Phenytoin C (mcg/ml)	Recommended ↑ dose (mg/day)
<7	↑ by 100
7-11	↑ by 50
>12	↑ by 30

http://www.ncbi.nlm.nih.gov/pubmed/15000924

1.1.1.4. Phenytoin DDIs

1.1.1.4. Quetiapine Case 1: Phenytoin DDIs

Do you need to worry about phenytoin pharmacokinetic DDIs?

1.1.1.4. Quetiapine Case 1: Phenytoin DDIs

Do you need to worry about phenytoin pharmacokinetic DDIs?

Yes.

1.1.1.4. Quetiapine Case 1: Phenytoin DDIs

Why?

1.1.1.4. Quetiapine Case 1: Phenytoin DDIs

Why?

Phenytoin is a major inducer.

1.1.1.4. Quetiapine Case 1: Phenytoin DDIs

- Potent inducers:
  - CYPs:
    - Massive effects: CYP2B6, CYP3A4
    - Moderate effects: CYP1A2, CYP2A6
    - Mild effects: CYP2C (CYP2C8, CYP2C9 & CYP2C19)
  - UGTs: several

1.1.1.4. Quetiapine Case 1: Phenytoin DDIs

- Time required (not well-studied):
  - Maximum: 1-2 weeks
  - De-induction: 1-2 weeks
  - Auto-induction: mild and not clinically relevant

1.1.1.4. Quetiapine Case 1: Phenytoin DDIs

Are phenytoin's inductive effects important for psychiatric drugs?

1.1.1.4. Quetiapine Case 1: Phenytoin DDIs

Are phenytoin's inductive effects important for psychiatric drugs?

Yes, very important.

1.1.1.4. Quetiapine Case 1: Phenytoin DDIs

- Induces metabolism of:
  - most antipsychotics
  - many antidepressants
  - many benzodiazepines
  - carbamazepine & lamotrigine

1.1.1.4. Quetiapine Case 1: Phenytoin DDIs

- Correction factors (described if ≥1.5):
  - 5 x: lurasidone, quetiapine
  - 3 x: haloperidol, paliperidone
  - 2-3 x: olanzapine
  - 2 x: aripiprazole, carbamazepine, iloperidone, lamotrigine, mirtazapine, risperidone, TCAs, topiramate
  - 1.5-2 x: clozapine
  - 1.5 x: felbamate

1.1.2. Phenytoin Pharmacodynamics

1.1.2. Quetiapine Case 1: Phenytoin Pharmacodynamics

What do you know about phenytoin pharmacodynamics?

1.1.2. Quetiapine Case 1: Phenytoin Pharmacodynamics

- Efficacy as an AED:
  - Phenytoin blocks voltage-dependent sodium channels in neurons.

http://www.ncbi.nlm.nih.gov/pubmed/22332980

1.2. Warfarin Pharmacology

1.2. Quetiapine Case 1: Warfarin

What do you know about warfarin pharmacology?

1.2. Warfarin Pharmacology

1.2.1. Warfarin Pharmacodynamics

1.2.2. Warfarin Pharmacokinetics

1.2.1. Warfarin Pharmacodynamics

1.2.1. Quetiapine Case 1: Warfarin Pharmacodynamics

- Racemic mix:
  - S-warfarin: most of the activity (5-6 times more active)
  - R-warfarin: little of the activity
  - Anticoagulant efficacy: Vitamin K antagonist

1.2.2. Warfarin Pharmacokinetics

1.2.2. Warfarin Pharmacokinetics

1.2.2.1. Warfarin Metabolism

1.2.2.2. Warfarin DDIs

1.2.2.3. Warfarin Monitoring

1.2.2.4. Warfarin Pharmacogenetics

1.2.2.1. Warfarin Metabolism

1.2.2.1. Quetiapine Case 1: Warfarin Metabolism

- S-warfarin metabolism:
  - mainly by CYP2C9
- R-warfarin metabolism:
  - CYP3A
  - CYP1A2
  - CYP2C19

1.2.2.2. Warfarin DDIs

1.2.2.2. Quetiapine Case 1: Warfarin DDIs

- Warfarin DDIs frequently have clinically relevant effects and are potentially lethal.
- Potent CYP2C9 inhibitors can ↓ warfarin metabolism.
- Potent CYP2C9 inducers can ↑ warfarin metabolism.

1.2.2.2. Quetiapine Case 1: Warfarin DDIs

- CYP2C9 inhibitors used in psychiatry:
  - potent:
    - fluvoxamine
    - valproate
  - moderate: fluoxetine

1.2.2.2. Quetiapine Case 1: Warfarin DDIs

- CYP2C9 inducers used in psychiatry:
  - carbamazepine

1.2.3. Warfarin Monitoring

1.2.3. Quetiapine Case 1: Warfarin Monitoring

What do you know about warfarin monitoring?

1.2.3. Quetiapine Case 1: Warfarin Monitoring

- Measured by the INR.
- INR values =

$$\frac{\text{patient prothrombin time}}{\text{mean normal prothrombin time}}$$

- INR recommended values:
  - vary per indication
  - usually 2.0 – 3.5 recommended range

1.2.3. Quetiapine Case 1: Warfarin Monitoring

- Serum warfarin Cs are not measured.
- However, you may want to remember warfarin as:
  - a narrow therapeutic window drug
  - with potentially lethal DDIs

1.2.4. Warfarin Pharmacogenetics

1.2.4. Quetiapine Case 1: Warfarin Pharmacogenetics

What do you know about warfarin pharmacogenetic testing?

1.2.4. Quetiapine Case 1: Warfarin Pharmacogenetics

- Clinical tests for polymorphic variations:
  - CYP2C9
  - VKORC1 (vitamin K epoxide reductase complex subunit 1)
- There are dose calculators using:
  - genetics: these 2 genes
  - co-medications:
    - inducers
    - inhibitors
  - personal factors:
    - age
    - height and weight
    - race

http://www.ncbi.nlm.nih.gov/pubmed/24251363

1.3. Olanzapine Pharmacology

1.3. Quetiapine Case 1: Olanzapine

Olanzapine	Phenytoin		Warfarin	
D	D	C	D(mg/wk)	INR
0	300	15.5	15	2.6
20 (6 weeks)	300	14.5	12.5	2.0
20	300	19.1	15	2.6
20	300	9.9	20	1.6

- Taking benztropine 0.5 mg/day.
- Olanzapine discontinued: no changes in INR.

1.3. Olanzapine Pharmacology

1.3.1. Olanzapine Pharmacokinetics

1.3.2. Olanzapine Pharmacodynamics

1.3.1. Olanzapine Pharmacokinetics

1.3.1. Quetiapine Case 1: Olanzapine Pharmacokinetics

What do you know about olanzapine pharmacokinetics?

1.3.1. Quetiapine Case 1: Olanzapine Pharmacokinetics

- Olanzapine metabolism:
  - mainly by CYP1A2
  - secondarily by UGT1A4

- As with most second-generation antipsychotics, olanzapine is:
  - not an inducer,
  - not a major inhibitor, but
  - possibly a competitive inhibitor.

1.3.2. Olanzapine Pharmacodynamics

1.3.2. Quetiapine Case 1: Olanzapine Pharmacodynamics

What do you know about olanzapine pharmacodynamics?

1.3.2. Quetiapine Case 1: Olanzapine Pharmacodynamics

- Olanzapine efficacy in psychosis (schizophrenia): D_2 antagonist
- No major effects on coagulation or platelet function are known.
- As with all antipsychotics, it has a black box warning for risk of death in elderly demented patients. Olanzapine use in dementia is an off-label indication.

1.4. Quetiapine Pharmacology

1.4. Quetiapine Case 1: Quetiapine

Quetiapine	Phenytoin		Warfarin	
D	D	C	D(mg/wk)	INR
0	300	12.1	19.5	2.7
200*	300	9.2	19.5	9.2

*After 2 weeks on quetiapine up to 200 mg/day.

1.4. Quetiapine Case 1: Quetiapine

- As INR ↑ from 2.7 to 9.2:
  - quetiapine was discontinued
  - warfarin was hold
    (not administered until INR normalized)
  - 2 injections of vitamin K_1 10 mg was given
  - injections produced a small amount of bleeding, along with bruising on the hand
- INR = 1.1 the next day
- The patient was stabilized on olanzapine.

1.4. Quetiapine Case 1: Quetiapine

Olanzapine	Phenytoin		Warfarin	
D	D	C	D(mg/wk)	INR
15*	400	17.7	21	1.6

*4 weeks on olanzapine and taking benztropine 0.5 mg/day.

1.4. Quetiapine Pharmacology

1.4.1. Quetiapine Pharmacokinetics

1.4.2. Quetiapine Pharmacodynamics

1.4.3. Quetiapine DI in This Case

1.4.1. Quetiapine Pharmacokinetics

1.4.1. Quetiapine Case 1: Quetiapine Pharmacokinetics

What do you know about quetiapine pharmacokinetics?

1.4.1. Quetiapine Case 1: Quetiapine Pharmacokinetics

- Quetiapine metabolism:
  - mainly by CYP3A
  - secondarily by CYP2D6
- As with most second-generation antipsychotics, quetiapine is:
  - not an inducer
  - not a major inhibitor, but
  - possibly a competitive inhibitor, particularly for CYP3A4

1.4.2. Quetiapine Pharmacodynamics

1.4.2. Quetiapine Case 1: Quetiapine Pharmacodynamics

What do you know about quetiapine pharmacodynamics?

1.4.2. Quetiapine Case 1: Quetiapine Pharmacodynamics

- Quetiapine efficacy in psychosis: D_2 antagonist (with low affinity and loose binding).
- No known major effects on coagulation or platelet function.
- As with all antipsychotics, it has a black box warning for risk of death in elderly demented patients. Quetiapine use in dementia is an off-label indication.

1.4.3. Quetiapine DI in This Case

1.4.3. Quetiapine Case 1: Quetiapine DI in This Case

- Quetiapine:
  - addition: ↑ INR
  - discontinuation: back to normal INRs
- Quetiapine appears to have caused a DI with warfarin.
- Mechanism:
  - pharmacodynamic mechanism: not known
  - pharmacokinetic mechanism: possible

1.4.3. Quetiapine Case 1: Quetiapine DI in This Case

- Competitive inhibition was possible:
  - At CYP3A4: quetiapine may inhibit R-warfarin metabolism.

1.5. Phenytoin's Role in This Case

1.5. Quetiapine Case 1: Phenytoin's Role

The INR was stable before and after quetiapine treatment and the patient was on phenytoin.

1.5. Quetiapine Case 1: Phenytoin's Role

Thus,
we conclude that phenytoin played no role in this DDI.

1.5. Quetiapine Case 1: Phenytoin's Role

Is this conclusion correct?

1.5. Quetiapine Case 1: Phenytoin's Role

Is this conclusion correct?

Certainly not.

1.5. Quetiapine Case 1: Phenytoin's Role

What is phenytoin's role?

1.5. Quetiapine Case 1: Phenytoin's Role

What is phenytoin's role?

Dr. de Leon is not sure, but it can be hypothesized.

1.5. Quetiapine Case 1: Phenytoin's Role

- Phenytoin metabolism by CYP2C9 was probably important.
  - Phenytoin competes with warfarin for CYP2C9 : warfarin D was in low range.

    http://www.ncbi.nlm.nih.gov/pubmed/19228618
- Phenytoin is an inducer:
  - but this was not evident: warfarin D was low
  - which may change the balance of CYP2C9 and CYP3A4 for warfarin metabolism.
- By correcting warfarin D according to the INR, the doctor was correcting for phenytoin's effects.

1.5. Quetiapine Case 1: Phenytoin's Role

- We can only hypothesize phenytoin's role. It is probably relevant by:
  - contributing to CYP2C9 inhibition and/or
  - induction, which may modify the metabolism of:
    - warfarin
    - (and/or quetiapine)
- In situations of polypharmacotherapy, it is not easy to interpret DIs.

1.6. Relevance of This Case Report

1.6. Relevance

1.6.1. Initial Recommendation at the Time of Publication (1999)

1.6.2. PubMed Search

1.6.3. Review of Articles

1.6.4. Generalization from a Case Report

1.6.1. Initial Recommendation at the Time of Publication (1999)

1.6.1. Quetiapine Case 1: Initial Recommendation

- The initial recommendation in the article regarding warfarin patients:
  - Consider whether adding quetiapine is really necessary; olanzapine did not ↑ the INR.
  - If it is necessary, monitor the INR closely.

1.6.2. PubMed Search (2016)

1.6.2. Quetiapine Case 1: PubMed Search

- Go to PubMed. http://www.ncbi.nlm.nih.gov/pubmed
- Type in the search box: "quetiapine and warfarin"
- On January 20, 2016, Dr. de Leon found 9 articles. Starting from the bottom, they are as follows.

1.6.2. Quetiapine Case 1: PubMed Search

- Number 9: http://www.ncbi.nlm.nih.gov/pubmed/10440472
  This is a case report.
- Number 8: http://www.ncbi.nlm.nih.gov/pubmed/11980386
  The abstract suggests it is not relevant.
- Number 7: http://www.ncbi.nlm.nih.gov/pubmed/12168506
  The abstract suggests it is not relevant.
- Number 6: http://www.ncbi.nlm.nih.gov/pubmed/16089244
  The abstract suggests it is not relevant.
- Number 5: http://www.ncbi.nlm.nih.gov/pubmed/19025425
  The abstract suggests it is not relevant.

1.6.2. Quetiapine Case 1: PubMed Search

- Number 4: http://www.ncbi.nlm.nih.gov/pubmed/21799620
  Title: “Drug interaction as cause of spontaneously resolving epidural spinal hematoma on warfarin therapy.”
  The abstract (and available pdf) suggest this was a case of polypharmacy and it is unclear whether quetiapine contributed or not.

1.6.2. Quetiapine Case 1: PubMed Search

- Number 3: http://www.ncbi.nlm.nih.gov/pubmed/21601733
  Yang & Liang, 2011
  Title: “Multiple intracerebral hemorrhages in an elderly patient after adding quetiapine to a stable warfarin regimen.”
  The abstract says, “…Here, we present an elderly male patient with dementia who developed multiple intracerebral hemorrhages (ICHs) 3 days after the addition of quetiapine to his stable warfarin regimen…”

1.6.2. Quetiapine Case 1: PubMed Search

- Number 2: http://www.ncbi.nlm.nih.gov/pubmed/23033232
  Nadkarni et al., 2012
  Title: “Drug-drug interactions between warfarin and psychotropics: updated review of the literature”
  The abstract states:
  “Psychotropics that pose a particular risk of increasing the INR when used with warfarin include fluoxetine, fluvoxamine, quetiapine, and valproic acid.”

1.6.2. Quetiapine Case 1: PubMed Search

- Number 1: http://www.ncbi.nlm.nih.gov/pubmed/24247877
  Chen et al., 2013
  Title: “Enhanced bleeding risk in an elderly dementia patient treated with warfarin and quetiapine.”
  There is no abstract.

1.6.3. Review of Articles

1.6.3. Review of Articles

1.6.3.1. Number 3: Case by Yang & Liang, 2011

1.6.3.2. Number 1: Case by Chen et al., 2013

1.6.3.3. Number 2: Review by Nadkarni et al., 2012

1.6.3.4. Another Warfarin Review: Holdbrook et al., 2005

1.6.3.1. Number 3: Case by Yang & Liang, 2011

http://www.ncbi.nlm.nih.gov/pubmed/21601733

1.6.3.1. Quetiapine Case 1: Case by Yang & Liang, 2011

- 71-year-old ♂ from Taiwan
- Diagnosis of dementia
- Medications:
  - warfarin for atrial fibrillation: INR 1.02-2.0
  - other co-medications:
    - atenolol 50 mg/d
    - lacidipine 4 mg/d
    - donepezil 5 mg/d
- After 3 days on quetiapine 12.5 mg/d:
  - an intracerebral hemorrhage developed
  - INR ↑ to 3.2

1.6.3.2. Number 1: Case by Chen et al., 2013

http://www.ncbi.nlm.nih.gov/pubmed/24247877

1.6.3.2. Quetiapine Case 1: Case by Chen et al., 2013

- 74-year-old ♂ from Taiwan
- Diagnosis of vascular dementia
- Medication:
  - quetiapine 400 mg/day for 3 years
- Developed peripheral vein thrombosis:
  - warfarin 1.25 mg/day for 1 month
- Admitted due to psychotic exacerbation:
  - INR was found to be 3.9
  - warfarin was stopped (and vitamin K added).
  - quetiapine was switched to amisulpride.
- Restarted with warfarin 1.25 mg/day with normal INRs on amisulpride.

1.6.3.3. Number 2: Review by Nadkarni et al., 2012

http://www.ncbi.nlm.nih.gov/pubmed/23033232

1.6.3.3. Quetiapine Case 1: Review by Nadkarni et al., 2012

- Based on 2 cases:
  - this case, and
  - case by Yang & Liang, 2011

    They consider quetiapine to “pose particular risk of increasing the INR”.
- They group quetiapine with some other inhibitors with more definitive data:
  - fluoxetine
  - fluvoxamine
  - valproic acid

1.6.3.4. Another Warfarin Review: Holdbrook et al., 2005

http://www.ncbi.nlm.nih.gov/pubmed/15911722

1.6.3.4. Quetiapine Case 1: Review by Holdbrook et al., 2005

- Yang & Liang, 2011, quote a 2005 warfarin review article, by Holbrook et al.
- Holbrook et al. had a different opinion: Tables 2 and 3 describe as “highly improbable” the quetiapine-warfarin DDI case described in this presentation.

1.6.3.4. Quetiapine Case 1: Review by Holdbrook et al., 2005

- There is a big difference between an evidence-based medicine approach used by Holbrook et al. versus a personalized medicine approach based on pharmacokinetic mechanisms used in this presentation.

1.6.3.4. Quetiapine Case 1: Review by Holdbrook et al., 2005

- Using an evidence-based medicine approach to verify the DDI described in this case requires studying a group of patients taking phenytoin and warfarin, randomizing them to quetiapine versus placebo, and following them prospectively.
- Such a study won't happen for economic (lack of funding) and ethical reasons (serious risk).

1.6.4. Generalization from a Case Report

1.6.4. Quetiapine Case 1: Generalization from a Case Report

- There are no case reports with other antipsychotics ↑ INR.
- Interpreting this case report, with a personalized medicine approach (pharmacological mechanisms), in 1999, Dr. de Leon recommended monitoring INR closely if the decision is made to add quetiapine to warfarin.

1.6.4. Quetiapine Case 1: Generalization from a Case Report

- In 2005, interpreting this case report, with an evidence-based medicine approach, Holbrook et al. recommended ignoring it (“highly improbable”).

1.6.4. Quetiapine Case 1: Generalization from a Case Report

When interpreting this case, what is best?
To give value to a personalized medicine approach
or to an evidence-based medicine approach?

1.6.4. Quetiapine Case 1: Generalization from a Case Report

- The best way is
  to frame the question
  as a risk-benefit analysis.

1.6.4. Quetiapine Case 1: Generalization from a Case Report

Let's imagine Holbrook et al.'s evidence-based approach is right, but you have followed Dr. de Leon's personalized medicine approach.
What are the risks and benefits?

1.6.4. Quetiapine Case 1: Generalization from a Case Report

- No benefits: quetiapine does not ↑ INR.
- Risks: you have wasted a few INRs by closely monitoring INR after adding quetiapine. The INRs were normal and you were overconcerned.

1.6.4. Quetiapine Case 1: Generalization from a Case Report

Let's imagine Dr. de Leon's personalized medicine approach is right, but you have followed Holbrook et al.'s evidence-based approach. What are the risks and benefits?

1.6.4. Generalization from a Case Report

- The risks of adding quetiapine to warfarin are demonstrated in 2 published cases by clinicians who ignored the risks:
  - Yang & Liang, 2011: the outcome was an intracerebral hemorrhage. http://www.ncbi.nlm.nih.gov/pubmed/21601733
  - Chen et al., 2013: ↑ INR was fortunately caught rapidly. http://www.ncbi.nlm.nih.gov/pubmed/24247877
- Benefits: avoiding these risky outcomes.

1.6.4. Generalization from a Case Report

Is this case report potentially relevant?

1.6.4. Generalization from a Case Report

Is this case report potentially relevant?

It depends on how you frame your thinking.

1.6.4. Generalization from a Case Report

- Dr. de Leon thinks the evidence-based medicine approach is very limited for identifying rare and potentially lethal ADRs.

  RCTs by pharmaceutical companies:
  - are short-term (weeks),
  - are small (hundreds of patients),
  - exclude patients with relevant
    - medical problems, or
    - co-medications.

1.6.4. Generalization from a Case Report

- Dr. de Leon thinks that you should pay attention to case reports for preventing rare and potentially lethal ADRs.

1.6. Quetiapine Case 1: Relevance

- If you are interested in differences between evidence-based and personalized-medicine approaches, see the presentation titled “Evidence-Based Medicine versus Personalized Medicine” or the editorial on which it is based. http://www.ncbi.nlm.nih.gov/pubmed/22367661

pre-printed free copy http://uknowledge.uky.edu/psychiatry_facpub/41/

Questions

- Please review the 10 questions on the pdf entitled "Questions on the Presentation Quetiapine Case 1 Warfarin".
- 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. A
2. B
3. D
4. D
5. B
6. C
7. D
8. B
9. B
10. A