Induction by Antiepileptic Drugs: An Update for Clinicians

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Conflicts of Interest: About the Field

1) Dr. de Leon is firmly convinced that the literature is contaminated by false negative findings. This means that Dr. de Leon believes that much published information is distorting clinical reality and the effect of inducers is much more important than what is believed.
2) Many studies were designed by pharmaceutical companies to provide negative results by using inducers in low doses or for short periods of time.
3) A 2-part editorial describes these ideas (reading it requires effort and basic pharmacological knowledge).

Part I on epilepsy: http://www.ncbi.nlm.nih.gov/pubmed/24525637

Free pre-publication version:
http://uknowledge.uky.edu/psychiatry_facpub/22/

Part II on bipolar disorder: http://www.ncbi.nlm.nih.gov/pubmed/24717257

Free pre-publication version:
http://uknowledge.uky.edu/psychiatry_facpub/24/

Controversial Ideas for Physicians

1) All of these ideas have gone though peer review but that is not a guarantee that they are true.
2) Average psychiatrists (and physicians) believe that drug-drug interactions are irrelevant. Dr. de Leon is firmly convinced by his clinical experience that adding potent inducers can make some drugs (e.g., antipsychotics) lose efficacy. He has also seen cases of several adverse drug reactions after discontinuing mild inducers (e.g., by lamotrigine after discontinuing oxcarbazepine http://www.ncbi.nlm.nih.gov/pubmed/17430308).

Controversial Ideas for Pharmacologists

Be aware that excellent pharmacologists have not been happy with some of the ideas described, including:

1)Valproate is an inducer.

2)Valproate can induce its own metabolism.

3)Extraordinarily high doses can be used in some patients (> 10,000 mg/day of valproate or >1600 mg/day of lamotrigine). When dealing with unusual subjects, Dr. de Leon believes that doses are not important (some patients need very high doses while others need very low doses); what is important is their serum concentrations. Dr. de Leon suggests you read articles (and/or PowerPoints) and make your own judgment about these cases.

Only time and independent replication will tell whether Dr. de Leon's practice is wrong or ahead of its time.

Learning Objectives

After completing this presentation, the participant should be able to:

1) Appreciate the relevance of potent inducers and how to apply dose correction factors to other drugs when co-prescribed with potent inducers.
2) Appreciate the possible relevance of mild inducers, which may include valproic acid.

Warning

This is an extraordinarily long presentation:

1) You may need to read it several times until you have become familiar with key aspects. More importantly, you need to practice every day and review all the drugs used when any of your patients are taking AED inducers in the context of polypharmacy.
2) Unfortunately, Dr. de Leon has decided to treat you like an adult and explain how little you know about induction.
3) If you think that this is complex, please see the AED pharmacokinetics presentation that reviews induction again and adds inhibition and protein binding. Real-life pharmacology with some of these drugs is very complex.

Warning about Lethality

1) If you feel this presentation is too complicated for your brain, you may want to stop prescribing carbamazepine, phenytoin, or valproate.
2) Use TDM when prescribing carbamazepine, phenytoin, or valproate.
3) Dr. de Leon has seen serious ADRs with these 3 AEDs prescribed by neurologists or psychiatrists who did not know what they were doing.
4) He has also reviewed deaths of patients caused by these 3 drugs, almost always in complex combinations.
5) Thinking that it will not happen to your patients is naïve. Dr. de Leon is always shocked by physicians' ability to deny that they have contributed to their patients' deaths. "Do not harm" appears to be a norm only for students.

Abbreviations

- ADR: adverse drug reactions
- AED: antiepileptic drugs
- AhR: aryl hydrocarbon receptor
- CAR: constitutive androstane receptor
- CYP: cytochrome P450
- DDI: drug-drug interaction
- ER: estrogen receptors
- GR: glucocorticoid receptor
- IV: intravenous
- MHD: monohydroxy derivate
- P-gp: P-glycoprotein
- PXR: pregnane X receptor
- TCA: tricyclic antidepressant
- TDM: therapeutic drug monitoring (blood levels)
- UGT: uridine diphosphate glucuronosyltransferases
- VPA: valproic acid

Dose Correction Factors

- Use a correction factor to multiply by the average dose to correct for DDIs.
- Two major types of pharmacokinetic DDIs:
  - Inducers: correction factor > 1
    (e.g., 2, multiply dose by 2)
  - Inhibitors: correction factor < 1
    (e.g., 0.5, multiply dose by 0.5)
- These are averages for the average patient. For individual patients it is better to use serum levels (pharmacologists call them therapeutic drug monitoring, TDM).

Dose Correction Factors: Risperidone as an Example

- Risperidone correction factors:
  - For inducer: carbamazepine = 2
  - For inhibitor: paroxetine = 0.5

- If in a typical patient you use 4 mg/d:
  - For a carbamazepine patient you should use 8 mg/d (4 mg/d x 2 = 8 mg/d)
  - For a paroxetine patient you should use 2 mg/d (4 mg/d x 0.5 = 2 mg/d)

Correction Factors are PROVISIONAL

- The correction factors will need to be updated as the literature gets better.
  Published correction factors for 3 antipsychotics when co-prescribing potent inducers have been updated from an article published in 2015

  http://www.ncbi.nlm.nih.gov/pubmed/25745819

  The new correction factor for:
  - clozapine: 1.5-2 x
  - olanzapine: 2-3 x
- The best way of avoiding using "imperfect" correction factors is using TDM (blood levels) to individualize your patient's dose.
  The case presentation lectures explain how to do it.

Relevance of Inducers

1. Potent Inducers
2. Mild Inducers
3. Endogenous Effects
4. Induced Pharmacokinetic Proteins
5. Pharmacological Mechanisms of Induction
6. Unusual Patients: Very Sensitive to Induction

Relevance of Inducers

1. Potent Inducers

1.1. Carbamazepine
1.2. Phenytoin
1.3. Phenobarbital
1.4. Effects on Drug Classes

2. Mild Inducers

2.1. Clobazam
2.2. Eslicarbazepine
2.3. Felbamate
2.4. Lamotrigine
2.5. Oxcarbazepine
2.6. Topiramate
2.7. Rufinamide
2.8. Vigabatrin\
2.9. VPA

Relevance of Inducers

3. Endogenous Effects

- 3.1. Sexual Hormones
- 3.2. Vitamin D
- 3.3. Thyroid Hormones
- 3.4. Lipid Metabolism
- 3.4. Folic Acid

4. Induced Pharmacokinetic Proteins

- 4.1. CYPs
- 4.2. UGTs
- 4.3. P-gp

5. Pharmacological Mechanisms of Induction

- 5.1. Nuclear Receptors
  - 5.1.1. PXR
  - 5.1.2. CAR
  - 5.1.3. ER
  - 5.1.4. GR
- 5.2. Acknowledging the Pharmacological Complexity of Induction

6. Unusual Patients: Very Sensitive to Induction

1. Potent Inducers

1. Potent Inducers

- 1.1. Carbamazepine
- 1.2. Phenytoin
- 1.3. Phenobarbital
- 1.4. Effects on Drug Classes

1.1. Carbamazepine

1.1. Carbamazepine

1.1.1. Metabolism

1.1.2. DDI: Inducer

1.1.1. Carbamazepine Metabolism

1.1.1. Carbamazepine Metabolism

- Major metabolite: 10,11 epoxide
  - Mainly by CYP3A4 (CYP2C8)
  - 40% metabolism (single dose)
    Probably more in repeated dosing
  - Metabolized by epoxide hydroxylase
- Aromatic hydroxylation (25%): CYP1A2
- Glucuronidation of the carbamoyl side chain by UGTs: presumably primarily by UGT2B7

1.1.1. Carbamazepine Metabolism

- Remember: Carbamazepine is metabolized by CYP3A4 and auto-induces its own metabolism.

1.1.2. Carbamazepine DDI: Inducer

1.1.2. Carbamazepine DDI: Inducer

- Not relevant as an inhibitor (rarely relevant)
- Potent inducer:
  - CYP:
    - Massive effects: CYP2B6, CYP3A4
    - Moderate effects: CYP1A2, CYP2A6
    - Mild effects: CYP2C (CYP2C8, CYP2C9 CYP2C19)
  - UGT: several (not well studied)

1.1.2. Carbamazepine DDI: Inducer

- Time required (not well-studied):
  - Onset: 1 week
  - Maximum: 3 weeks
  - De-induction: 3 weeks
  - Auto-induction (CYP3A4): 3-5 weeks

    Steady state requires 3-5 weeks.

1.1.2. Carbamazepine DDI: Inducer

- Correction factors (described if ≥1.5):
  - 10 x: bupropion: Never use
  - 5 x (or higher): lurasidone, quetiapine
  - 5 x: sertraline
  - 3 x: haloperidol, paliperidone
  - 2-3 x: olanzapine
  - 2 x: aripiprazole, iloperidone, mirtazapine, risperidone, TCAs, theophylline, topiramate
  - 1.5 x: felbamate, lamotrigine

1.1.2. Carbamazepine DDI: Inducer

- Remember:
  Carbamazepine is a potent inducer.

1.2. Phenytoin

1.2. Phenytoin

1.2.1. Metabolism

1.2.2. DDI: Inducer

1.2.1. Phenytoin Metabolism

1.2.1. Phenytoin Metabolism

- Para-hydroxylated:
  - CYP2C9
  - Lower importance: CYP2C19
- Other less important enzymes may be:
  - CYP2C8
  - CYP3A

1.2.1. Phenytoin Metabolism

- Phenytoin is a peculiar drug, which is defined by pharmacologists as follows:
  - Has a narrow therapeutic window
  - Follows nonlinear pharmacokinetics:
    - dose-dependent and
    - capacity-limited
- The presentation on AED pharmacokinetics will try to "confuse" you by explaining that you need to understand protein binding to prescribe phenytoin.

1.2.1. Phenytoin Metabolism

- A peculiar drug, as explained for a clinician:
  - ≥ 20 mcg/ml: bad news
    - saturation of the enzymes and
    - ↑ half-life: requires the complete discontinuation of phenytoin for ≥ 2-3 days until normal metabolism levels < 20 mcg/ml
  - close to 20 mcg/ml: be very careful
    - ↑ dose: risky
    - adding CYP2C9/2C19 drugs: risky

1.2.1. Phenytoin Metabolism

- Remember:
  CYP2C9/CYP2C19
  At high levels ($\geq$ 20 mcg/ml), phenytoin inhibits its own metabolism.

1.2.2. Phenytoin DDI: Inducer

1.2.2. Phenytoin DDI: Inducer

- Can inhibit CYP2C9/C19 (saturation)
- Potent inducer:
  - CYP:
    - Massive effects: CYP2B6, CYP3A4
    - Moderate effects: CYP1A2, CYP2A6
    - Mild effects: CYP2C (CYP2C8, CYP2C9 CYP2C19)
  - UGT: several
- More potent than carbamazepine

1.2.2. Phenytoin DDI: Inducer

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

1.1.3. Phenytoin DDI: Inducer

- 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

1.1.3. Phenytoin DDI: Inducer

- Remember:

  Phenytoin is a potent inducer and can easily intoxicate your patients.

1.3. Phenobarbital

1.3. Phenobarbital

1.3.1. Metabolism

1.3.2. DDI: Inducer

1.3.1. Phenobarbital Metabolism

1.3.1. Phenobarbital Metabolism

- Eliminated unchanged in urine (20-50%)
- Metabolism:
  - parahydroxyphenobarbital:
    - major: CYP2C9
    - others: CYP2C19 and CYP2E1
  - phenobarbital N-glucoside

1.3.1. Phenobarbital Metabolism

- Auto-induction is not described in textbooks:
  - very long half-life (2-6 days) (weeks to steady state)
  - due to this long-life it is very difficult to study auto-induction

1.3.1. Phenobarbital Metabolism

- Remember:
  Phenobarbital eliminated:
  by kidney
  and CYP2C9 metabolism.

1.3.2. Phenobarbital DDI: Inducer

1.3.2. Phenobarbital DDI: Inducer

- Not relevant as an inhibitor (rarely relevant)
- Potent inducer:
  - CYP:
    - Massive effects: CYP2B6, CYP3A4
    - Moderate effects: CYP1A2, CYP2A6
    - Mild effects: CYP2C (CYP2C8, CYP2C9 CYP2C19)
  - UGT: bilirubin (UGT1A1)
    possibly other UGTs

1.3.2. Phenobarbital DDI: Inducer

- Time required (not well-studied):
  - Onset: 1 week
  - Maximum: 2-3 weeks
  - De-induction: 2-3 weeks
  - Auto-induction: ?

    Steady state requires up to 1 month

1.3.3. Phenobarbital DDI: Inducer

- Correction factors:
  - 1.5 x: clozapine
- Almost no studies
- Use phenytoin correction factors.

1.3.3. Phenobarbital DDI: Inducer

- Remember: Phenobarbital is a potent inducer.

1.4. Effects on Drug Classes

1.4. Effects on Drug Classes

- Very few individual drugs have been studied.
- Predictions can be made based on the specific metabolism of each drug.
- Potent inducers have massive effects on CYP3A4 drugs.

1.4. Effects on Drug Classes

1.4.1. Antipsychotics

1.4.2. Antidepressants

1.4.3. Benzodiazepines

1.4.4. Oral Contraceptives

1.4.5. Others

1.4.1. Antipsychotics: Induction

1.4.1. Antipsychotics: Induction

- Most sensitive (>5x):
  quetiapine, lurasidone
- Moderately sensitive (>2-4x):
  aripiprazole, clozapine, haloperidol, iloperidone, olanzapine, paliperidone, risperidone
- Asenapine: not well-studied (moderate effects would not be surprising).
- Small effects (not clinically relevant)
  amisulpride, ziprasidone

1.4.2. Antidepressants: Induction

1.4.2. Antidepressants: Induction

- Do not use (>10 x dose): bupropion
- Most sensitive (not well-studied):

  sertraline, reboxetine, trazadone, vilazodone
- Moderately sensitive (>2-4x):

  agomelatine, mirtazapine, TCAs, vortioxetine
- Be careful (not studied, possibly moderate):

  desvenlafaxine, duloxetine, venlafaxine
- Small effects (rarely clinically relevant)

  citalopram, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, paroxetine

1.4.3. Benzodiazepines: Induction

1.4.3. Benzodiazepines: Induction

- Dependent on CYP3A4: do not use:
  alprazolam, midazolam, triazolam
- Not well-studied but possibly moderate:
  - dependent on UGTs: lorazepam, oxazepam
  - dependent on CYP2C19/34A (be careful with phenytoin CYP2C9 inhibition):
    clobazam, diazepam
- Clonazepam (partly dependent on CY3A4):
  correction factor 1.5-1.33 x dose.

1.4.3. Benzodiazepines: Induction

- Nonbenzodiazepine hypnotics ($GABA_A$ receptor positive allosteric modulators):
  - Do not use (dependent on CYP3A4):
    - eszopiclone
    - zolpidem
  - CYP3A4 is a minor pathway:
    - zaleplon

1.4.4. Oral Contraceptives: Induction

1.4.4. Oral Contraceptives: Induction

- Estrogen is partly dependent on CYP3A4: Do not use on female patients taking highly potent inducers.
- Prescribing information about potent and mild CYP3A4 inducers:
  - Warn about pregnancy risk.

1.4.5. Other drugs: Induction

1.4.5. Other Drugs: Induction

- Statins:
  - Do not use (dependent on CYP3A4):

    atorvastatin, lovastatin, simvastatin
  - Less sensitive (not well-studied):

    fluvastatin, pitavastatin, pravastatin, rosuvastatin
- CYP3A4 is important for many:
  - calcium channel blockers
  - immunosuppressants

  Check with pharmacy before co-prescribing.

2. Mild Inducers

(Other authors do not used this terminology to group these drugs.)

Warning

This section is very long and describes some AEDs rarely used by psychiatrists.

Please skip the AEDs that you may not consider relevant for your clinical practice.

2. Mild Inducers

	Potent	Mild
Effect size	Potent	Mild
Individuals	In all	Variable
Dose effects	No*	Yes
Inhibition		Can obscure it
Chronology		
Onset	Weeks	Weeks
Maximum	Weeks	Weeks to months
De-induction	Weeks	Weeks to months

* In therapeutic doses

2. Mild Inducers:

2.1. Clobazam
2.2. Eslicarbazepine
2.3. Felbamate
2.4. Lamotrigine
2.5. Oxcarbazepine
2.6. Topiramate
2.7. Rufinamide
2.8. Vigabatrin
2.9. VPA

2.1. Clobazam

2.1. Clobazam

2.1.1. Metabolism

2.2.2. DDI

2.2.1. Clobazam Metabolism

2.2.1. Clobazam Metabolism

- Major (94%) metabolite and active: N-desmethylclobazam (norclobazam):
  - mainly by CYP3A4
  - minor: CYP2C19 and CYP2B6
- Another minor pathway: hydroxylation by CYP2C18 and CYP2C19.
- N-desmethylclobazam (norclobazam):
  - mainly by CYP2C19
  - minor: CYP3A4
- Mild auto-induction

2.1.1. Clobazam Metabolism

- Remember:
  Clobazam is metabolized by CYP3A4 and its metabolite by CYP2C9.

2.2.2. Clobazam DDI

2.2.2. Clobazam DDI

- Mild inducer (compound and metabolite):
  - CYP3A4
  - UGT1A1 (bilirubin)

  It is concentration-dependent.

  Maximal induction may take months until the metabolite's effects are completed.
- Mild inhibitor (N-desmethylclobazam):
  - CYP2C19
  - CYP2D6
  - UGTs (UGT1A4, UGT1A6, UGT2B4)

2.2. Eslicarbazepine

2.2. Eslicarbazepine

2.2.1. Metabolism

2.2.2. DDI

2.2.1. Eslicarbazepine Metabolism

2.2.1. Eslicarbazepine Metabolism

- Eslicarbazepine acetate: pro-drug
- 95% hydrolyzed during first-pass metabolism (liver/gut) to eslicarbazepine (or S-licarbazepine or S-MHD).
- 5% is oxidized to
  - oxcarbazepine and
  - R-licarbazepine (or R-MHD)
- S-licarbazepine eliminated in urine:
  - 2/3 as S-licarbazepine
  - 1/3 as glucuronide conjugates (UGT1A1)

2.2.1. Eslicarbazepine Metabolism

- No auto-induction

2.2.1. Eslicarbazepine Metabolism

- Remember:

  Acetate is hydrolyzed to eslicarbazepine (active).

2.2.2. Eslicarbazepine DDI

2.2.2. Eslicarbazepine DDI

- Mild inducer:
  - CYP3A4
  - UGTs

  It is concentration-dependent for oral contraceptives.

- Moderate inhibitor:
  - CYP2C9
  - CYP2C19

2.3. Felbamate

2.3. Felbamate

2.3.1. Metabolism

2.3.2. DDI

2.3.1. Felbamate Metabolism

2.3.1. Felbamate Metabolism

- In the absence of potent inducers:
  - 40-60% is excreted by the kidneys.
  - The rest is metabolized:
    - hydroxylation: CYP3A & CYP2E1
    - glucuronidation

  Auto-induction has not been studied.
- In the presence of potent inducers:
  - CYP3A4 becomes more important.

  Auto-induction is not likely to be relevant.

2.3.1. Felbamate Metabolism

- Remember: Kidney elimination and CYP3A4.

2.3.2. Felbamate DDI

2.3.2. Felbamate DDI

- Mild inducer:
  - CYP3A4

  There is very limited information on clinical effects.
- Moderate inhibitor:
  - CYP2C19
  - ß-oxidation (VPA metabolism)

2.4. Lamotrigine

2.4. Lamotrigine

2.4.1. Metabolism

2.4.2. DDI

2.4.1. Lamotrigine Metabolism

2.4.1. Lamotrigine Metabolism

- Glucuronidation: 65-90%
  - UGT1A4: major enzyme
  - UGT2B7: may or may not be relevant, depending on the articles.
- Urine excretion:
  - lamotrigine and
  - its metabolites
- Mild auto-induction:
  - within the first 2 weeks
  - not seen in pateints on potent inducers

2.4.1. Lamotrigine Metabolism

- Remember:
  Lamotrigine is glucuronidated and this is inhibited by VPA.

2.4.2. Lamotrigine DDI

2.4.2. Lamotrigine DDI

- Mild inducer:
  - UGTs
  - possibly of quetiapine
- Mild inhibitor:
  - possibly of olanzapine metabolism only in non-smokers

2.5. Oxcarbazepine

2.5. Oxcarbazepine

2.5.1. Metabolism

2.5.2. DDI

2.5.1. Oxcarbazepine Metabolism

2.5.1. Oxcarbazepine Metabolism

- Oxcarbazepine is a pro-drug. It is reduced by a cytosol arylketonereductase to MHD (80% S-MHD & 20% R-MHD).
- MHD (or licarbazepine) is cleared by:
  - glucuronidation and, less so,
  - oxidation to an inactive metabolite.
- Renal excretion: major (80%) route
  - glucuronides of MHD (40%),
  - unchanged MHD (27%),
  - MHD/oxcarbazepine conjugates (13%), and
  - 10,11-dihydroxymetabolite.

2.5.1. Oxcarbazepine Metabolism

- No auto-induction

- When you order oxcarbazepine TDM, the lab will only provide concentration of MHD (oxcarbazepine is a pro-drug).

2.5.1. Oxcarbazepine Metabolism

- Remember: Oxcarbazepine is a pro-drug activated to MHD (or licarbazepine).

2.5.2. Oxcarbazepine DDI

2.5.2. Oxcarbazepine DDI

- Mild inducer in high doses (≥1200 mg/day):
  - CYP3A4

    A recent case of quetiapine induction has been described: http://www.ncbi.nlm.nih.gov/pubmed/26469302
  - UGT1A4

    It is similar to carbamazepine but less potent. De-induction may take up to 2 months.
- Moderate inhibitor:
  - CYP2C19

2.5.2. Oxcarbazepine DDI

- Remember: oxcarbazepine (≥1200 mg/day) can be an inducer (CYP3A4 and UGT).

2.5.2. Oxcarbazepine DDI

Dr. de Leon's clinical practice:

- In occasional cases that Dr. de Leon has seen, in which oxcarbazepine caused clinically-relevant induction, the correction factors appear similar to carbamazepine. He cannot rule out that these were unusually sensitive patients.

2.6. Rufinamide

2.6. Rufinamide

2.6.1. Metabolism

2.6.2. DDI

2.6.1. Rufinamide Metabolism

2.6.1. Rufinamide Metabolism

- Rufinamide
  - Extensively metabolized by carboxylesterases
  - 2-4% unchanged in urine and feces
- No auto-induction

2.6.1. Rufinamide Metabolism

- Remember: Rufinamide is not metabolized by CYPs.

2.5.2. Rufinamide DDI

2.6.2. Rufinamide DDI

- Mild inducer:
  - CYP3A4
  - UGTs
- Mild inhibitor:
  - CYP2E1

2.7. Topiramate

2.7. Topiramate

2.7.1. Metabolism

2.7.2. DDI

2.7.1. Topiramate Metabolism

2.7.1. Topiramate Metabolism

- In the absence of inducers:
  - Mainly eliminated unchanged in the urine
  - 20% metabolized by CYPs
- In the presence of potent inducers:
  ↑ clearance x 2 due to ↑ of CYP metabolism
- No auto-induction

2.7.1. Topiramate Metabolism

- Remember about topiramate elimination:

	POTENT INDUCER	
	Absent	Present
Elimination	Kidney elimination CYP relatively small	↑ CYP metabolism
Doses		Much higher needed

2.7.2. Topiramate DDI

2.7.2. Topiramate DDI

- Mild inducer in high doses (≥ 400 mg/day):
  - CYP3A4
  - β-oxidation (VPA)

- Moderate inhibitor:
  - CYP2C19
  - VPA glucuronidation

2.7.2. Topiramate DDI

- Remember:

  Topiramate (≥ 400 mg/day) can be an inducer (CYP3A4).

2.8. Vigabatrin

2.8. Vigabatrin

2.8.1. Metabolism

2.8.2. DDI

2.8.1. Vigabatrin Metabolism

2.8.1. Vigabatrin Metabolism

- In the absence of inducers:
  - Mainly eliminated unchanged in the urine
  - <10% metabolized
- In the presence of potent inducers:
  ↑ clearance x 2 due to ↑ of CYP metabolism
- No auto-induction

2.8.1. Vigabatrin Metabolism

- Remember about vigabatrin (and topiramate):

	POTENT INDUCER	
	Absent	Present
Elimination	Kidney elimination CYP relatively small	↑ CYP metabolism
Doses		Much higher needed

2.8.2. Vigabatrin DDI

2.8.2. Vigabatrin DDI

- Mild inducer:
  - CYP2C9: not evident until weeks 5-6
- No relevant inhibitor

2.9. VPA

2.9. VPA

2.9.1. Metabolism

2.9.2. DDI

2.9.1. VPA Metabolism

2.9.1. VPA Metabolism

- Complex metabolism:
  - UGTs
    - hepatic (& intestinal): UGT1A3, UGT1A4, UGT1A6, UGT1A9 & UGT2B7
    - intestinal (UGT1A8 and UGT1A10).
  - β-oxidation as a fatty acid
  - CYP (CYP2C9, CYP2C19 and CYP2A6)
- It changes according to dose:
  - In low doses: β-oxidation is most important.
  - In therapeutic doses: UGT is most important.

2.9.1. VPA Metabolism

- Auto-induction (not well-studied):
  - by UGTs in rats
  - β-oxidation in human volunteers
  - Dr. de Leon's experience: some individuals are very sensitive.

2.9.1. VPA Metabolism

- Remember:

VPA metabolism is complex:

Doses:	Low	Therapeutic
β-oxidation	Most important	Second
UGTs	Second	First
CYPs	Minor	Minor

2.8.2. VPA DDI

2.8.2. VPA DDI

- Traditionally considered an inhibitor:
  - CYP2C9
  - Epoxide hydroxylase (carbamazepine)
  - Several UGTs
  - N-glucosidation (phenobarbital)

2.8.2. VPA DDI

- Inducer of:
  - its own metabolism in some individuals
  - irinotecan (UGT1A1)
  - aripiprazole
  - vitamin D (in vitro study)
  - clozapine/olanzapine:
    - concentration-related
    - possibly influenced by smoking
    - confounded by competitive inhibition, so the net effect may be inhibition or induction.

2.8.2. VPA DDI

Dr. de Leon's clinical practice:

- VPA auto-induction is relevant in rare cases.
- Clozapine/olanzapine. VPA can be:
  - a mild inducer,
  - rarely a potent inducer, or
  - a mild inhibitor.

The AED pharmacokinetic presentation will explain the role of protein binding and free concentrations.

2.8.2. VPA DDI

- Remember:
  VPA can be an inducer (olanzapine and clozapine) and an auto-inducer (replication needed).

3. Endogenous Effects

3. Endogenous Effects

- Known for 30 years: inducers ↑ metabolism of exogenous compounds (xenobiotics).
- Known for only 10 years: inducers ↑ metabolism of endogenous compounds and change homeostasis of:
  - Sexual hormones
  - Vitamin D
  - Thyroid hormones
  - Lipid metabolism
  - Folic acid

3. Endogenous Effects

- In the clinical environment, a continuum exists from exogenous to endogenous.
- Sexual hormones, for example:
  - Oral contraceptives (exogenous): agreement that potent and mild inducers ↑ metabolism.
  - Substituting sexual hormones (deficit): some information that higher doses may be needed (absent homeostatic mechanisms).
  - Endogenous sexual hormones with normal endocrinology: potent inducers rarely cause relevant changes (corrected by normal homeostasis).

3. Endogenous Effects

3.1. Sexual Hormones

3.2. Vitamin D

3.3. Thyroid Hormones

3.4. Lipid Metabolism

3.4. Folic Acid

3.1. Sexual Hormones

3.1. Sexual Hormones

- Many sexual hormones (including major estrogens) are dependent for their metabolism on CYP3A4.
- Oral contraceptives should not be used in females taking potent AED inducers.
- Moreover, 5 AED mild inducers: clobazam, eslicarbazepine, oxcarbazepine, topiramate & rufinamide have been approved with warnings about pregnancy risk in women using oral contraceptives as the only contraceptive method

3.1. Sexual Hormones

- The AED potent inducers have demonstrated inductive effects when sexual hormones are administered for treating hypopituitarism.

- The effect of potent inducers on endogenous ♀ & ♂ sexual hormones appears more limited, although in rare cases:
  - menstrual disorders in ♀, and
  - ↓ sexual potency in ♂.

3.1. Sexual Hormones

- Remember sexual hormones can ALSO be inducers or inhibitors of AED metabolism.
- These effects are relevant in pregnancy as there is a massive ↑ in female sexual hormones.
  - ↑ activity:
    - CYP2B6
    - CYP2C9
    - CYP2D6 (no induction)
    - CYP3A4
    - Lamotrigine glucuronidation
  - ↓ activity:
    - CYP1A2
    - CYP2C19

3.2. Vitamin D

3.2. Vitamin D

- Vitamin D is a derivative compound of cholesterol, and its metabolism is mediated by CYPs.
- AED potent inducers definitively can cause osteoporosis.
- Some mild inducers oxcarbazepine, topiramate & VPA may also cause osteoporosis, due to the induction of vitamin D.

3.3. Thyroid Hormones

3.3. Thyroid Hormones

- UGTs are fundamental for their metabolism.
- Potent inducers can interfere with thyroid function by ↑ thyroid hormone metabolism. In Dr. de Leon's experience, thyroid abnormalities are more likely when the endogenous feedback is impaired and frequent when thyroid medication is administered exogenously and the body cannot compensate.
- Oxcarbazepine has also occasionally been associated with hypothyroidism.

3.4. Lipid Metabolism

3.4. Lipid Metabolism

- Potent inducers:
  - can interfere with the metabolism of cholesterol and other complex lipids,
  - have been associated with hyperlipidemia,
  - but mechanisms are poorly understood.

3.5. Folic Acid

3.5. Folic Acid

- Potent inducers have an effect on folic acid, but it is not clear that it is due to induction. Phenytoin may be an inhibitor of the folic acid transporter.
- Phenytoin is clearly associated with gingival overgrowth.
- Phenytoin and phenobarbital can cause macrocytic anemia.
- Controversial: potent inducers, by influencing folic acid metabolism, may contribute to hyperhomocysteinemia (↑ atherosclerosis risk).

4. Induced Pharmacokinetic Proteins

Warning

This section is

on

basic pharmacology

and may be toxic

for your psychiatric brain.

Please skip it if you are

worried about toxicity.

4. Induced Pharmacokinetic Proteins

- The main mechanism for ↑ enzyme activity is: ↑ synthesis of the metabolic enzyme.
  Inducers ↑ the synthesis of metabolic enzymes. This is why there is a delay in onset and termination of the effect of inducers.
- Two rare exceptions:
  - ↑ enzyme activity by ↓ degradation of the metabolic enzyme: CYP2E1.
  - CYP2D6 cannot be induced.
    ↑ CYP2D6 activity in pregnancy: explained by ↓ of a CYP2D6 repressor.

4. Induced Pharmacokinetic Proteins

- Remember: Inducers↑ synthesis of metabolic enzymes (delay in onset/termination).

4. Induced Pharmacokinetic Proteins:

4.1. CYP

4.2. UGT

4.3. P-gp

4.1. CYP Induction

4.1. CYP Induction

- CYP names include a number for the family, a letter for the subfamily and then another number for the specific isoenzyme.
- Two groups:
  - The first 3 CYP families (CYP1, CYP2, CYP3):
    - are mainly located in the liver and
    - are involved in the metabolism of xenobiotics: medications, and carcinogens
    - have a limited role in endogenous metabolism
  - Others families (CYPs ≥ 4) are only involved in endogenous metabolism.

4.1. CYP Induction

- The major CYPs in the first 3 families are the major oxidative (Phase I) enzymes.
  - In neuropsychopharmacology:
    - CYP1A2
    - CYP2B6
    - CYP2C9
    - CYP2C19
    - CYP2D6
    - CYP3A4

4.1. CYP Induction

- Sensitive to induction (not described in other articles):
  - Massive (++++)
    - CYP2B6
    - CYP3A4
  - Moderate (++)
    - CYP1A2
  - Mild (+)
    - CYP2C9
    - CYP2C19
- It cannot be induced: CYP2D6.

4.2. UGT Induction

4.2. UGT Induction

- UGTs are the most important of the conjugation enzymes (traditionally called Phase II metabolic enzymes).
- They are the main metabolic enzymes for a few:
  - antipsychotics: asenapine
    haloperidol (possibly)
  - AEDs: lamotrigine
    retigabine (ezogabine)
  - benzodiazepines: lorazepam
    oxazepam
- UGT knowledge is 10-15 years behind that of CYPs.

4.2. UGT Induction

.■ 4 factors contributing to this neglect include:

1) The difficulty of developing analytic methods to measure glucuronides
2) The overlapping activity of UGTs and the lack of selective probes
3) The complexity of the glucuronidation cycle (comprising reabsorption throughout the enterohepatic cycle and participation in deconjugation by β-glucuronidases; including those present in bacteria)
4) Endogenous compounds that are frequently substrate, inhibitor or inducer UGTs.

4.2. UGT Induction

- The most important UGTs (substrates):
  - Expressed in the liver:
    - UGT1A1 (bilirubin)
    - UGT1A3
    - UGT1A4 (lamotrigine)
    - UGT1A6
    - UGT1A9
    - UGT2B7
    - UGT2B15 (lorazepam)
  - Non-expressed in the liver, mainly in the gut:
    - UGT1A8
    - UGT1A10

4.2. UGT Induction

- Remember:
  We have limited understanding of UGT induction.

4.3. P-gp Induction

4.3. P-gp Induction

- P-gp is the best studied transporter.
- Functionally, transporters are classified as:
  - uptake or influx transporters,
    mediating the uptake of drugs into cells.
  - efflux transporters,
    mediating the export of drugs or
    drug metabolites out of cells.
- P-gp is an efflux transporter.

4.3. P-gp Induction

- P-gp gene nomenclature is confusing:
  - The P-gp gene was called the multidrug resistant protein 1 (MDR1) gene.
  - It was found to be part of a very large family of ATP binding transporter genes, some of which are involved in human genetic disorders, and was renamed ATP-binding cassette sub-family B member 1 (ABCB1).

4.3. P-gp Induction

- P-gp plays a central role in the absorption, distribution and excretion of a wide variety of drugs.
- It acts as a natural defense mechanism against several drugs.
- P-gp is expressed in several tissues:
  - intestine: ↓ absorption
  - kidney: ↑ urine elimination
  - liver: ↑ bile elimination
  - brain: ↓ brain penetration
  - placenta

4.3. P-gp Induction

- CYP3A4 and P-gp have similar regulations and site actions and share many:
  - substrates
  - inhibitors
  - possible inducers
- The P-gp articles on neuropsychopharmacology provide a very confusing picture for clinicians regarding:
  - AEDs
  - antidepressants
  - antipsychotics

4.3. P-gp Induction

- Remember:
  P-gp information is not ready for clinical use.

5. Pharmacological Mechanisms of Induction

Warning

This section
is on
nuclear receptors
that are not described
in psychiatric textbooks.
Be careful, nuclear receptors may
be a delusion that Dr. de Leon
shares with pharmacologists.

5. Mechanisms of Induction

- Increased synthesis is frequently mediated by a group of receptors that activate genes in the nucleus of the cell and are usually called nuclear receptors.
- As nuclear receptors have the ability to directly bind to DNA and regulate the expression of adjacent genes, they are considered transcription factors.
- The aryl hydrocarbon receptor (AhR) is not a nuclear receptor, but it is part of another superfamily of transcription factors.

5. Mechanisms of Induction

- The AhR is not important for AED induction.
- The AhR is important for induction by:
  - Omeprazole
  - Broccoli (cruciferous vegetables)
  - Polycyclic aromatic hydrocarbons (PAHs) present in
    - smoke
    - roasted coffee
    - charbroiled meat, bind to AhR, which is important for the induction of
      - CYP1A2
      - some UGTs

5. Mechanism Induction

- Remember: Smoking is an inducer but acts on different receptors than AEDs.

5. Mechanisms of Induction

5.1. Nuclear Receptors

5.2. Acknowledging Pharmacological Complexity

5.1. Nuclear Receptors

5.1. Nuclear Receptors

- The most important nuclear receptors involved in induction are:
  - the pregnane X receptor (PXR)
  - the constitutive androstane receptor (CAR)
  - the glucocorticoid receptor (GR)
  - the estrogen receptors (ERs).

  They are important in the induction of some enzymes during pregnancy.

5.1. Nuclear Receptors

- One of the problems for clinicians trying to become familiar with this research area is its complexity.
- The role of nuclear receptors goes beyond the effects of xenobiotics such as
  - drugs
  - pesticides
  - environmental pollutants
  - carcinogens
  - some complex nutrients (e.g., flavonoids)

5.1. Nuclear Receptors

- As a matter of fact, these receptors regulate one of the most complex biosynthesis processes, the transformation of cholesterol into multiple complex biological agents:
  - bile acids
  - corticoids
  - sexual hormones
  - vitamin D
- There are important differences with rodent nuclear receptors.
- The literature is complex and confusing.

5.1. Nuclear Receptors

- Remember:

  Nuclear receptors are important for induction (the literature is very confusing).

5.1. Nuclear Receptors

5.1.1. PXR

5.1.2. CAR

5.1.3. ER

5.1.4. GR

5.1.1. PXR

5.1.1. PXR

- PXRs are mainly located in:
  - Liver
  - Small intestine
- Inducers that activate PXRs:
  - Carbamazepine, phenytoin, and phenobarbital
  - VPA (possibly)
  - Rifampin
  - St. John's wort
- They are important for the induction of:
  - CYP2 and CYP3 families
  - some UGTs

5.1.2. CAR

5.1.2. CAR

- CARs are mainly located in:
  - liver
  - kidney
- Inducers that activate PXRs:
  - Phenytoin and phenobarbital
  - VPA (possibly)
- They are important for the induction of:
  - CYP2B6
  - CYP3A4

5.1.3. GR

5.1.3. GR

- Corticoids such as:
  - dexamethasone
  - prednisolone
  - methylprednisolone

  They are mild/moderate inducers.
- Their actions are mediated by:
  - GR
  - PXR

5.1.4. ER

5.1.4. ER

- According to in vitro studies:
  - ↑ levels of estrogens (x100) in pregnancy activate:
    - ER and
    - CAR,

    which have synergistic effects, ↑ CYP2B6 expression
  - ER may be partly responsible for the lamotrigine induction seen in pregnancy.

5.2. Acknowledging the Pharmacological Complexity of Induction

5.2. Pharmacological Complexity

- Using correction factors assumes that the patient is average.
- Many patients are not average (use TDM).

5.2. Pharmacological Complexity

- Induction is influenced by:
  - Route: IV is much less sensitive to induction
  - Genetics: If you do not have an enzyme,
    (you are a poor metabolizer)
    the enzyme cannot be induced.
  - The presence of inhibitors
  - The presence of other inducers
  - Other pharmacological mechanisms

5.2. Pharmacological Complexity

- If you are not an expert in pharmacology, do not combine:
  - carbamazepine and phenytoin
  - carbamazepine and VPA
  - phenytoin and VPA

  You need to consider:
  - induction
  - inhibition
  - protein binding
  - pharmacodynamics

6. Unusual Patients: Very Sensitive to Induction

6. Unusual Patients

- Dr. de Leon believes nuclear receptors may be important in understanding 6 of his most unusual patients.
- Induction in some of these patients appears to influence several enzymes and, in one case, CYP and UGTs.
- Nuclear receptors are at superior levels of regulation and can influence multiple enzymes. Genetic abnormalities at nuclear receptors may explain 6 cases.

6. Unusual Patients

6.1. High Doses for Lamotrigine and Lorazepam (1 Case)

6.2. High VPA Dose (2 Cases)

6.3. High Doses for VPA and CYP3A4 Drugs (1 Case)

6.4. High Dose for CYP3A4 Drugs (1 Case)

6.5. High Clozapine Dose (1 Case)

Warning

In the future, Dr. de Leon plans to develop individual presentations for each of these cases.

Please see

Clozapine Case 5: High Dose presentation

for Case 5 of this section.

6.1. High Doses for Lamotrigine and Lorazepam (1 case)

6.1. High Lamotrigine & Lorazepam Doses

- Normal drug metabolism for:
  - phenytoin and phenobarbital: CYP2C9
  - lacosamide: CYP2C19
  - quetiapine under induction: CYP3A4
- Abnormal drug metabolism for:
  - lamotrigine 1600 mg/day: UGT1A4
    4 times faster than normal
  - lorazepam: UGT2B15 and UGT1A3
    He tolerated >20 mg/day
    In the university hospital: 4 mg IV (seizures)
    Very low concentration on 8 mg/day.

6.1. High Lamotrigine & Lorazepam Doses

- In this patient:
  - CYP induction appeared normal
  - Abnormally high UGT induction at several UGTs

- It does not appear to be a problem at the level of the metabolic enzymes but above them (at the nuclear receptors?).

6.2. High VPA Dose (2 cases)

6.2. High VPA Doses (2 Cases)

- Need to keep ↑ VPA doses to get VPA therapeutic concentrations.
  After a ↑ dose: VPA concentrations were therapeutic but then further ↑ dose needed:
  - 1 up to 4000 mg/day
  - 1 up to 10,000 mg/day.

6.2. High VPA Doses (2 Cases)

- It is unclear why only some patients were very sensitive to VPA auto-induction.

- It does not appear to be a problem at the level of the metabolic enzymes but, rather, above them (at the nuclear receptors?).

6.3. High Doses for VPA and CYP3A4 Drugs (1 Case)

6.3. High Doses for VPA & CYP3A4 Drugs (1 Case)

- The patient was very sensitive to CYP3A4 induction:
  - Carbamazepine auto-induction: high doses (1500-2000 mg/day) were required to get therapeutic concentrations.
  - Diazepam was intensely induced by phenytoin: serum concentrations were not detectable on diazepam 30 mg/day
  - Quetiapine was intensely induced by phenytoin

6.3. High Doses for VPA & CYP3A4 Drugs (1 Case)

- The patient was very sensitive to VPA auto-induction:
  - Auto-induction on valproic acid: high doses (5250 mg/day) were needed to get therapeutic VPA concentrations.
  - No auto-induction on divalproex sodium: normal doses (2000 mg/day) were needed to get therapeutic VPA concentrations.

  (see Valproate Case 3 in PowerPoint).
- Normal metabolism for clozapine and olanzapine on VPA.

6.3. High Doses for VPA & CYP3A4 Drugs (1 Case)

- It is unclear why this patient was very sensitive to VPA auto-induction in reference to only one formulation. He was also very sensitive to CYP3A4 induction.
- It does not appear to be a problem at the level of the metabolic enzymes but, rather, above them (at the nuclear receptors?).

6.4. High Doses for CYP3A4 Drugs (1 Case)

6.4. High Doses for CYP3A4 Drugs (1 Case)

- Very sensitive to induction by carbamazepine:
  - carbamazepine: 2800 mg/day to get therapeutic concentrations
  - risperidone: > 40 mg/day (4 x faster than normal risperidone metabolism). In the US it is rare to have risperidone doses > 10 mg/day. When the patient was taking VPA and not carbamazepine, he appeared to only need 10 mg/day of risperidone.
- A high volume of distribution (very tall and high BMI) contributed to the need for high doses.

6.5. High Clozapine Dose (1 Case)

Warning

Described in detail in
Clozapine Case 5:
High Dose Presentation

6.5. High Clozapine Dose (1 Case)

- He was very sensitive to VPA induction:
  - Needed 1300 mg/day of clozapine to get therapeutic concentrations (maximum recommended clozapine dosage in the US: 900 mg/day).
  - Clozapine induction by VPA was possibly dose related (more correctly defined as related to higher free VPA concentration). It was only present during aspirin co-prescription.

References for Inducers at PubMed

1) 2015 article http://www.ncbi.nlm.nih.gov/pubmed/25745819 on induction (Part I) with updates on correction factors Free pdf in PubMed.
2) 2015 article http://www.ncbi.nlm.nih.gov/pubmed/26111722 on induction (Part II) with reviews on nuclear receptors. Free pdf in PubMed.
3) 2013 article http://www.ncbi.nlm.nih.gov/pubmed/24113673 with 1 case needing high clozapine doses.
4) 2015 article http://www.ncbi.nlm.nih.gov/pubmed/26000191 with 3 cases needing > 4000 mg/day of VPA. Free pdf in PubMed.
5) Article with 1 case needing > 1600 mg/day of lamotrigine http://www.ncbi.nlm.nih.gov/pubmed/26448400

Free versions of articles (some in Word)

1) 2015 article http://uknowledge.uky.edu/psychiatry_facpub/22/ on induction (Part I) with updates on correction factors.
2) 2015 article http://uknowledge.uky.edu/psychiatry_facpub/24/ on induction (Part II) with reviews on nuclear receptors.
3) 2013 article http://www.ncbi.nlm.nih.gov/pubmed/24113673 with 1 case needing high clozapine doses.
4) 2015 article http://uknowledge.uky.edu/psychiatry_facpub/3/ with 3 cases needing > 4000 mg/day of VPA.
5) Article with 1 case needing > 1600 mg/day of lamotrigine. The Word version will be available in the future.

Thank you

for surviving so much pharmacology

Answers

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