Lamotrigine Case 1 Stevens-Johnson Syndrome 2-02-16

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1. Lamotrigine Case 1

Bipolar Disorders 9:310-313, 2007

http://www.ncbi.nlm.nih.gov/pubmed/17430308

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 lamotrigine safety, one must consider Pharmacodynamics and pharmacokinetics
3. Show familiarity with the Stevens-Johnson Syndrome

Abbreviations

- ADR: adverse drug reaction
- AED: anti-epileptic drug
- DDI: drug-drug interaction
- ID: intellectual disability
- RCT: randomized controlled trial
- TDM: therapeutic drug monitoring
- UGT: uridine 5’-diphosphate glucuronosyltransferase

Lamotrigine Case 1

1.0. Lamotrigine Efficacy and Safety

1.1. Stevens-Johnson Syndrome: Diagnosis

1.2. Rechallenge After Rash

1.3. Case Description

Lamotrigine Case 1

1.0. Lamotrigine Efficacy and Safety

- 1.0.1. Efficacy
- 1.0.2. Safety

1.1. Stevens-Johnson Syndrome: Diagnosis

- 1.1.1. Benign Rash
- 1.1.2. Web Cases with Pictures

1.2. Rechallenge After Rash

1.3. Case Description

- 1.3.1. Case Description
- 1.3.2. Medications
- 1.3.3. Outcome
- 1.3.4. Interpretation

1.0. Lamotrigine Efficacy and Safety

Book Chapter 9: A Practitioner's Guide for Prescribing Lamotrigine in Adults with Intellectual Disabilities

http://link.springer.com/chapter/10.1007/978-1-4614-2012-5_9

1.0. Lamotrigine Efficacy and Safety

1.0.1. Efficacy
1.0.2. Safety

1.0.1. Lamotrigine Efficacy

1.0.1. Lamotrigine Efficacy

What do you know about lamotrigine efficacy?

1.0.1. Lamotrigine Efficacy

- Lamotrigine:
  - is an AED with a broad profile.
  - is approved in bipolar disorder for:
    - maintenance treatment and
    - depressive phase.
  - is not efficacious for mania.

1.0.2. Lamotrigine Safety

1.0.2. Lamotrigine Safety

What do you know about lamotrigine ADRs?

1.0.2. Lamotrigine Safety

1.0.2.1. Common ADRs
1.0.2.2. Relatively Uncommon ADRs
1.0.2.3. Metabolic Syndrome
1.0.2.4. Potentially Lethal ADRs

1.0.2.1. Lamotrigine: Common ADRs

1.0.2.1. Lamotrigine Safety: Common ADRs

- Common (>10% in RCTs) ADRs:
  - In epilepsy RCTs:
    - nausea
  - In bipolar RCTs:
    - headaches, and
    - nausea
- In a meta-analysis of RCTs of new AEDs, lamotrigine was associated with ↑ risk of:
  - dizziness
  - ataxia

http://www.ncbi.nlm.nih.gov/pubmed/18262442

1.0.2.2. Lamotrigine: Uncommon ADRs

1.0.2.2. Lamotrigine Safety: Uncommon ADRs

- Relatively uncommon (<10% in RCTs) ADRs include neuropsychiatric ADRs:
  - ↓ alertness: (when starting any AED, you should caution patients about performing tasks that require alertness (e.g., driving, operating machinery) until they know how they are influenced by lamotrigine.
  - Low cognitive effects: fewer cognitive effects than
    - the first-generation AEDs, and
    - topiramate. http://www.ncbi.nlm.nih.gov/pubmed/17125413
  - ■ Low risk of causing psychiatric ADRs:
    - definitively has less risk than levetiracetam and is a better choice for epilepsy in ID.

http://www.ncbi.nlm.nih.gov/pubmed/19016830

1.0.2.3. Lamotrigine: Metabolic Syndrome

1.0.2.3. Lamotrigine Safety: Metabolic Syndrome

- Good profile regarding metabolic syndrome
- No relevant weight changes in:
  - epilepsy http://www.ncbi.nlm.nih.gov/pubmed/18047602
  - bipolar disorder http://www.ncbi.nlm.nih.gov/pubmed/14756579

1.0.2.4. Lamotrigine: Potentially Lethal ADRs

1.0.2.4. Potentially Lethal ADRs

1.0.2.4.1. Suicidal Behavior
1.0.2.4.2. Stevens-Johnson Syndrome

1.0.2.4.1. Lamotrigine: Suicidal Behavior

1.0.2.4.1. Lamotrigine Case 1: Suicide

- Regarding potentially lethal ADRs, remember that the FDA requires a warning in the prescribing information that all AEDs ↑ the risk for suicidal ideation and behavior.
- In the FDA meta-analysis of AED RCTs, lamotrigine was associated with an increased risk for suicidal ideation and behavior, odds ratio 2.1 (1.03-4.0). http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-01-FDA.pdf
- However, reviews by experts suggest that lamotrigine may have a positive profile in epileptic patients for its potential to display antidepressant properties. http://www.ncbi.nlm.nih.gov/pubmed/17253878

1.0.2.4.2. Lamotrigine: Stevens-Johnson Syndrome

1.0.2.4.2. Lamotrigine Case 1: Stevens-Johnson Syndrome

- Lamotrigine has been associated with Stevens-Johnson Syndrome.
- The serious, potentially life-threatening rash follows a spectrum:
  - from Severe Bullous Erythema Multiforme
  - to Stevens-Johnson Syndrome
  - to Toxic Epidermal Necrolysis in the most severe cases.
- It prominently affects the neck or upper trunk.

1.0.2.4.2. Lamotrigine Case 1: Stevens-Johnson Syndrome

- Levels of severity: http://www.ncbi.nlm.nih.gov/pubmed/19153164
  - Stevens-Johnson Syndrome: <10% detachment of the total body surface area.
  - Toxic Epidermal Necrolysis: >30% detachment of the total body surface area. 40% of cases are fatal.
  - Intermediate cases are called Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis.

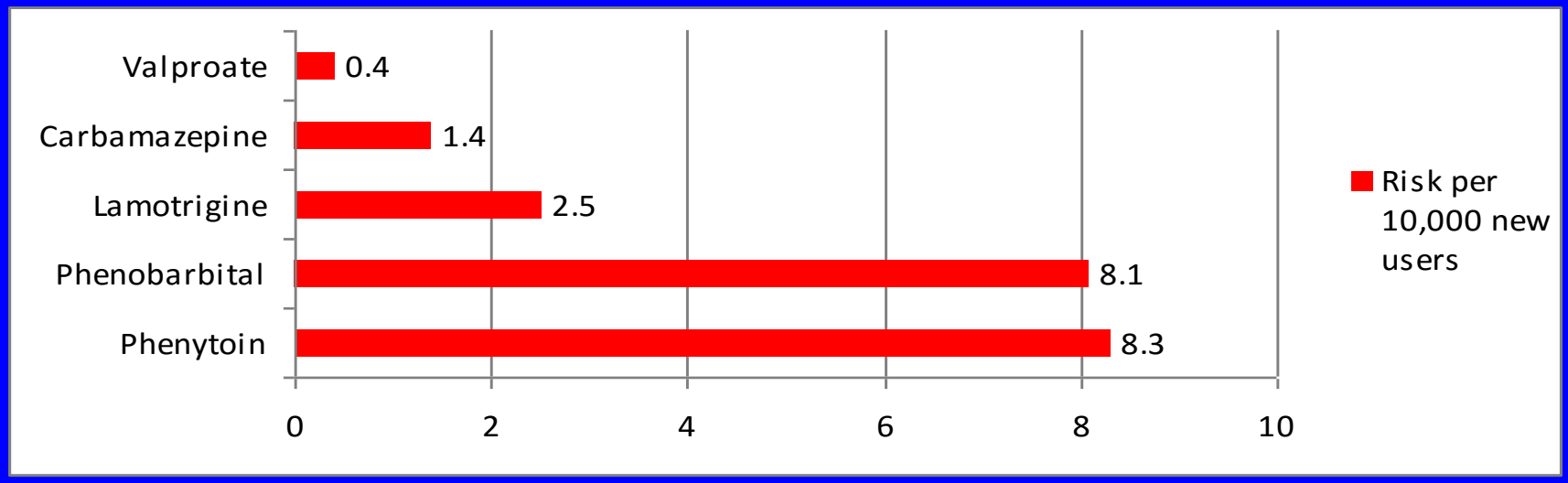
1.0.2.4.2. Lamotrigine Case 1: Stevens-Johnson Syndrome

- Many AEDs have been associated with Stevens-Johnson Syndrome.
- In fact, in a large German pharmacoepidemiologal study, lamotrigine had an intermediate rate.

http://www.ncbi.nlm.nih.gov/pubmed/15824335

1.0.2.4.2. Lamotrigine Case 1: Stevens-Johnson Syndrome

Pharmacoepidemiology Study of Stevens-Johnson in Germany



http://www.ncbi.nlm.nih.gov/pubmed/15824335

1.0.2.4.2. Lamotrigine Case 1: Stevens-Johnson Syndrome

Prescribing Information Changes

- Experience with Stevens-Johnson Syndrome in patients with epilepsy led to lamotrigine dosage guideline changes in 1994:
  - a lower starting dose, and
  - a slower dose titration.

- ↓ Incidence of Stevens-Johnson Syndrome: http://www.ncbi.nlm.nih.gov/pubmed/10534214
  - from 0.3% (3/1000) in adult RCTs
  - ↓ to 0.1% (1/1000) after dosage guideline changes

1.0.2.4.2. Lamotrigine Case 1: Stevens-Johnson Syndrome

- Risk factors associated with occurrence of serious rashes on lamotrigine: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=32038
  - exceeding the recommended starting dose or dose escalation
  - co-prescription with valproate
  - being a child

1.0.2.4.2. Lamotrigine Case 1: Stevens-Johnson Syndrome

- ADRs are usually classified according to 2 extremes:
  - dose-related
  - idiosyncratic and unpredictable; not dose-related. Many appear to be immunological ADRs.
- Most cases of AED-induced Stevens-Johnson Syndrome are idiosyncratic. It is assumed that prescribers cannot do anything to prevent them unless some specific vulnerability factor is identified, such as genetic variation.

1.0.2.4.2. Lamotrigine Case 1: Stevens-Johnson Syndrome

- Lamotrigine-induced Stevens-Johnson Syndrome has peculiar pharmacokinetics:
  - It is frequently associated with rapid titration. This has a dose-related component, which means ↑ risk due to:
    - rapid dose escalation
    - ↓ metabolism by inhibitor: valproate

    On one hand, inducers ↓ risk. But the other side of the coin is that stopping an inducer may ↑ risk, as it is the equivalent of a dose escalation.
- The pharmacodynamic mechanisms of lamotrigine-induced Stevens-Johnson Syndrome are not well-understood but probably involve the immune system.

1.1. Stevens-Johnson Syndrome: Diagnosis

1.1. Stevens-Johnson Syndrome: Diagnosis

1.1.1. Lamotrigine Benign Rash
1.1.2. Web Cases with Pictures

1.1.1. Lamotrigine Benign Rash

1.1.1. Lamotrigine Case 1: Benign Rash

- Lamotrigine can also cause a benign rash.
- Its incidence rates (around 5%) have remained stable despite changes in the recommended dosing schedule. This suggests it may have a different pathophysiology.

1.1.1. Lamotrigine Case 1: Benign Rash

- Benign Rash and Stevens-Johnson Syndrome can be distinguished by 3 characteristics: http://www.ncbi.nlm.nih.gov/pubmed/17430308
  - Time evolution: early in benign rash
  - Systemic involvement: absent in benign rash
  - Type of rash:
    more spotty and less confluent in benign rash

1.1.1. Lamotrigine Case 1: Benign Rash

- Time evolution:
  - Benign Rash: often occurs within 5-10 days of first exposure and improves within one to two weeks
  - Stevens-Johnsons Syndrome: often occurs much later, after the first 5 days and up to months after initiation.

1.1.1. Lamotrigine Case 1: Benign Rash

- Systemic involvement :
  - Benign Rash:
    - no systemic involvement
    - normal blood counts
    - normal liver and kidney function tests
  - Stevens-Johnson Syndrome:
    - Ulcers in mucosal areas (eyes, lips or mouth) also often occur.
    - Systemic symptoms such as fever, malaise, anorexia, lymphadenopathy are often present.
    - Hematological, hepatic and kidney tests can be abnormal.

1.1.1. Lamotrigine Case 1: Benign Rash

- Type of rash:
  - Benign Rash:
    - spotty,
    - raised,
    - erythematous,
    - non-confluent and
    - non-tender
  - Stevens-Johnsons Syndrome:
    - more likely confluent and widespread,
    - not raised,
    - purpuric and tender and
    - includes blistering with varying degrees of skin detachment

1.1.2. Web Cases with Pictures

1.1.2. Web Cases with Pictures

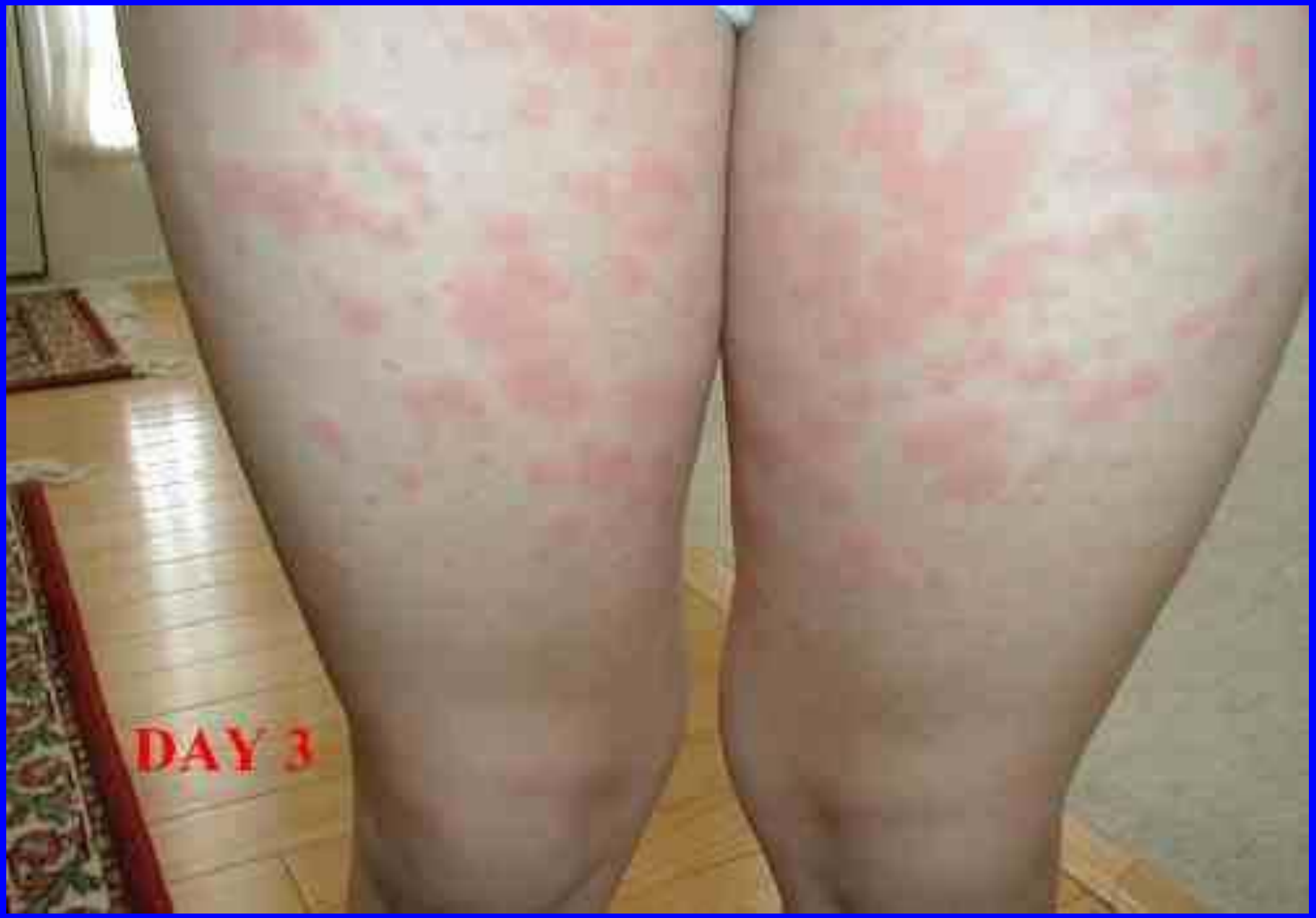
1.1.2.1. Pictures: Benign Rash
1.1.2.2. Pictures: Stevens-Johnson Syndrome
1.1.2.3. Pictures: Toxic Epidermal Necrolysis
1.1.2.4. Pictures: Fatal Toxic Epidermal Necrolysis
1.1.2.5. More Web Pictures

1.1.2.1. Pictures: Benign Rash

1.1.2.1. Lamotrigine Case 1: Benign Rash Picture

- Benign Rash on the 3rd day on lamotrigine: picture taken from the Web (a patient discussion forum)
  http://www.depressionforums.org/forums/index.php?app=core&module=attach&section=attach&attach_rel_module=post&attach_id=58

1.1.2.1. Lamotrigine Case 1: Benign Rash Picture



1.1.2.2. Pictures: Stevens-Johnson Syndrome

1.1.2.2. Lamotrigine Case 1: Stevens-Johnson Syndrome Picture

- Two pictures were taken from a free article available on PubMed.

  http://www.ncbi.nlm.nih.gov/pubmed/15843672

- A 22-year-old ♀ had a seizure disorder.
- 5 weeks after starting on a gradually increasing dose of lamotrigine while tapering off valproate,
- She went to the emergency room after having a rash for 3 days and fever for 1 day.

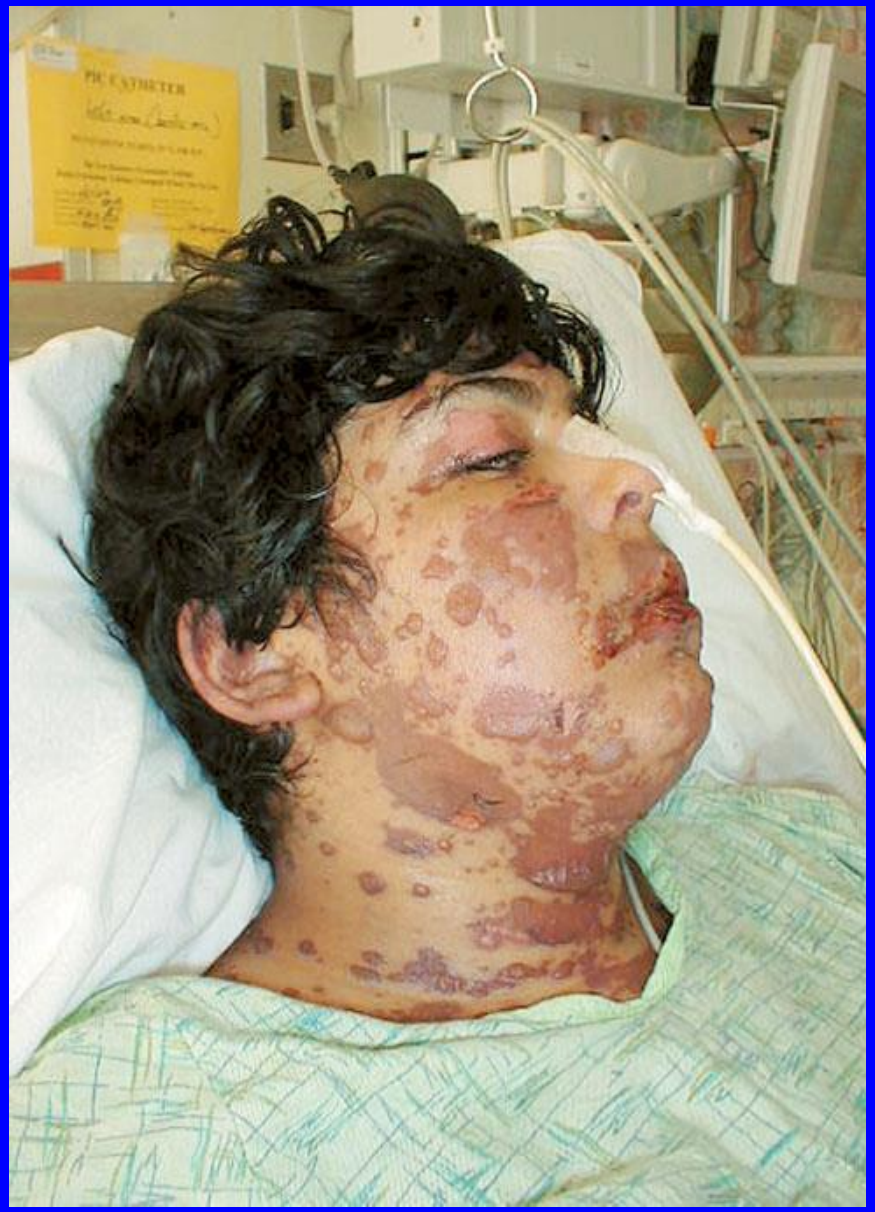
1.1.2.2. Lamotrigine Case 1: Stevens-Johnson Syndrome Picture

- Symptoms and signs:
  - The rash:
    - began as a maculopapular distribution on the neck and chest
    - rapidly progressed to target lesions and bullae involved on all skin surfaces
    - in the end only the scalp was spared.
  - Painful erosions of the mucosa of
    - the conjunctiva,
    - mouth, and
    - vagina
  - Fevers as high as 40.5°C (104.9°F).

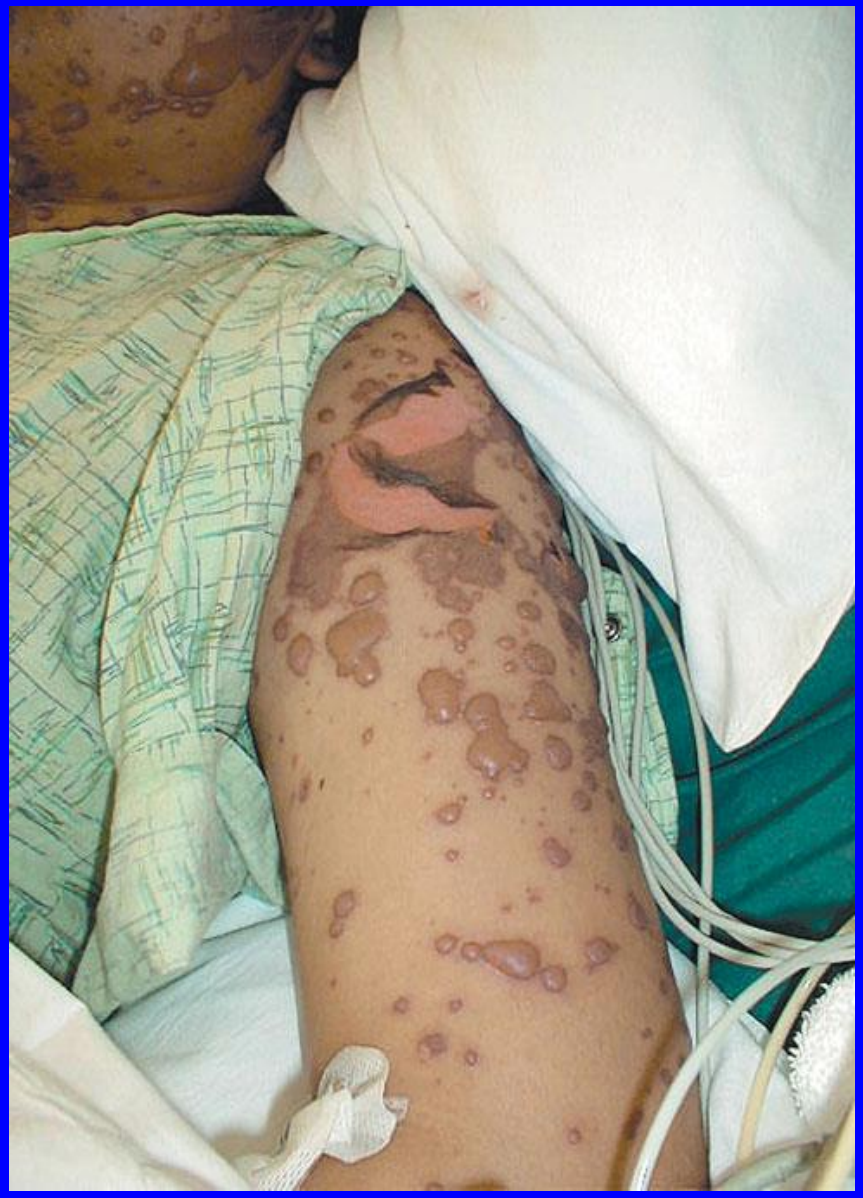
1.1.2.2. Lamotrigine Case 1: Stevens-Johnson Syndrome Picture

- A diagnosis of Stevens–Johnson Syndrome was made (<10% detachment).
- Both AEDs were discontinued.

1.1.2.2. Lamotrigine Case 1: Stevens-Johnson Syndrome Picture



1.1.2.2. Lamotrigine Case 1: Stevens-Johnson Syndrome Picture



1.1.2.3. Pictures:
Toxic Epidermal Necrolysis

1.1.2.3. Lamotrigine Case 1: Toxic Epidermal Necrolysis

- A free article is available on PubMed:
  http://www.ncbi.nlm.nih.gov/pubmed/17673387
- Pharmacological history:
  - The patient was on valproic acid for 15 years.
  - Lamotrigine 25 mg/day was added.
  - 1 week later he developed
    - a facial edema, and
    - pain in the throat.
  - 5 days later the patient
    - was shivering
    - with widespread erythema.

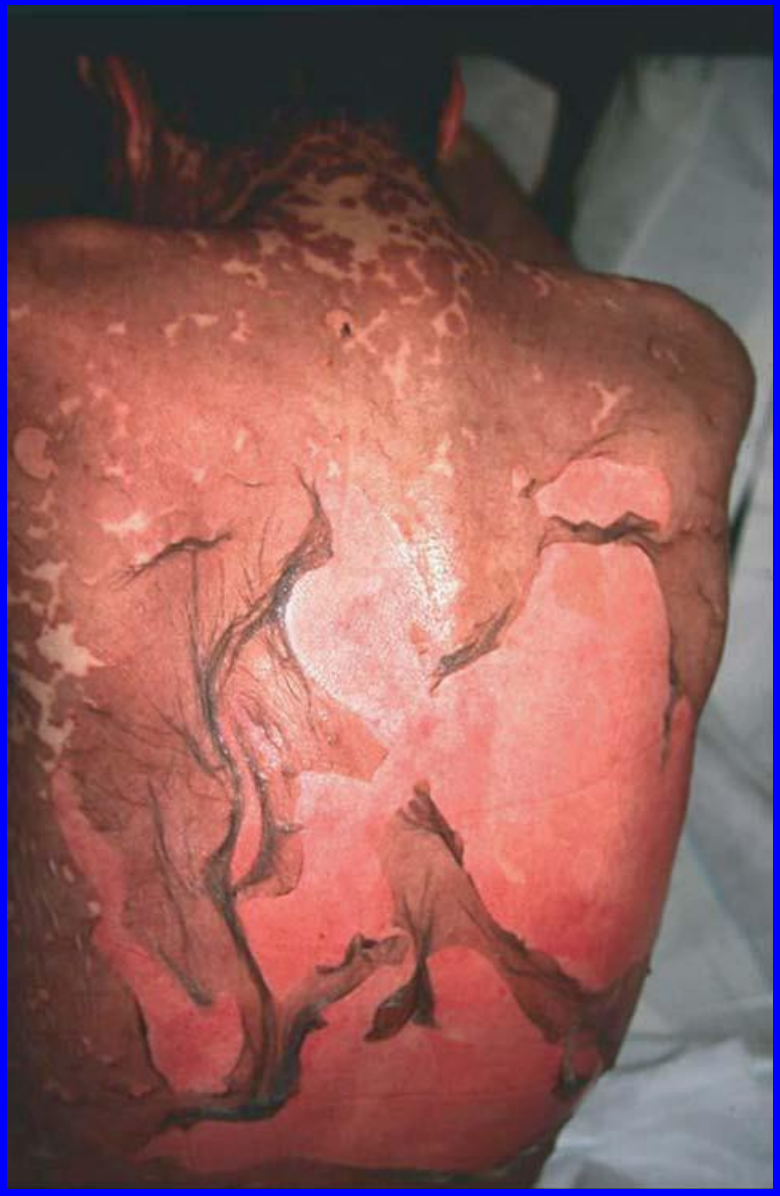
1.1.2.3. Lamotrigine Case 1: Toxic Epidermal Necrolysis

- Diagnosis of Toxic Epidermal Necrolysis:
  - skin detachment >30%
  - ulcerations in the oral cavity
  - fever (39 °C; 102.2 °F);
  - bilateral submandibular lymphadenopathy
  - ↑ erythrocyte sedimentation rate
  - ↑ liver enzymes
  - eosinophilia

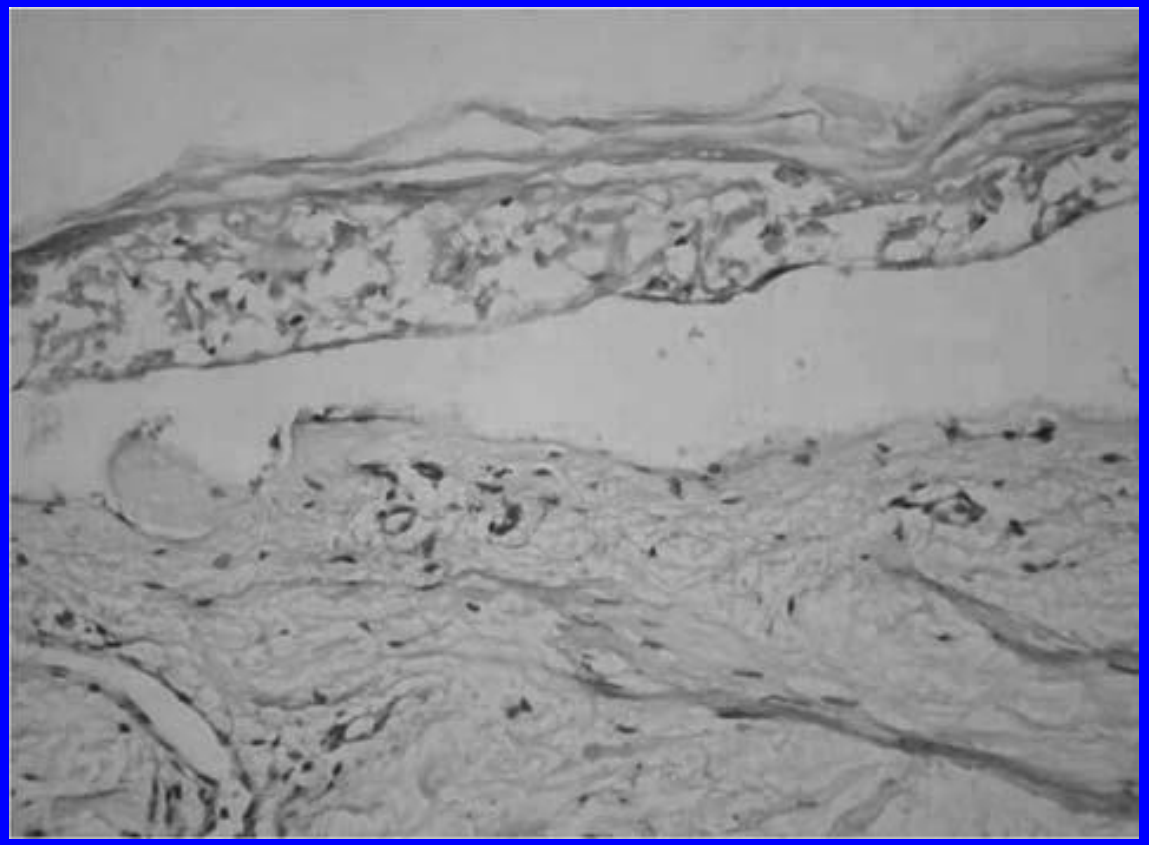
1.1.2.3. Lamotrigine Case 1: Toxic Epidermal Necrolysis

- Worsening after hospitalization:
  - Massive peeling of the skin:
    - face,
    - trunk, and
    - extremities
  - Hemorrhagic blisters on
    - hands and
    - feet
  - Widespread erosions on mucosae:
    - genital
    - oral; hemorrhagic crusts covered the lips
    - conjunctiva: vision was impaired by purulent exudation & conjunctival reaction

1.1.2.3. Lamotrigine Case 1: Toxic Epidermal Necrolysis



1.1.2.3. Lamotrigine Case 1: Toxic Epidermal Necrolysis Total necrosis and complete separation of the epidermis from the underlying dermis

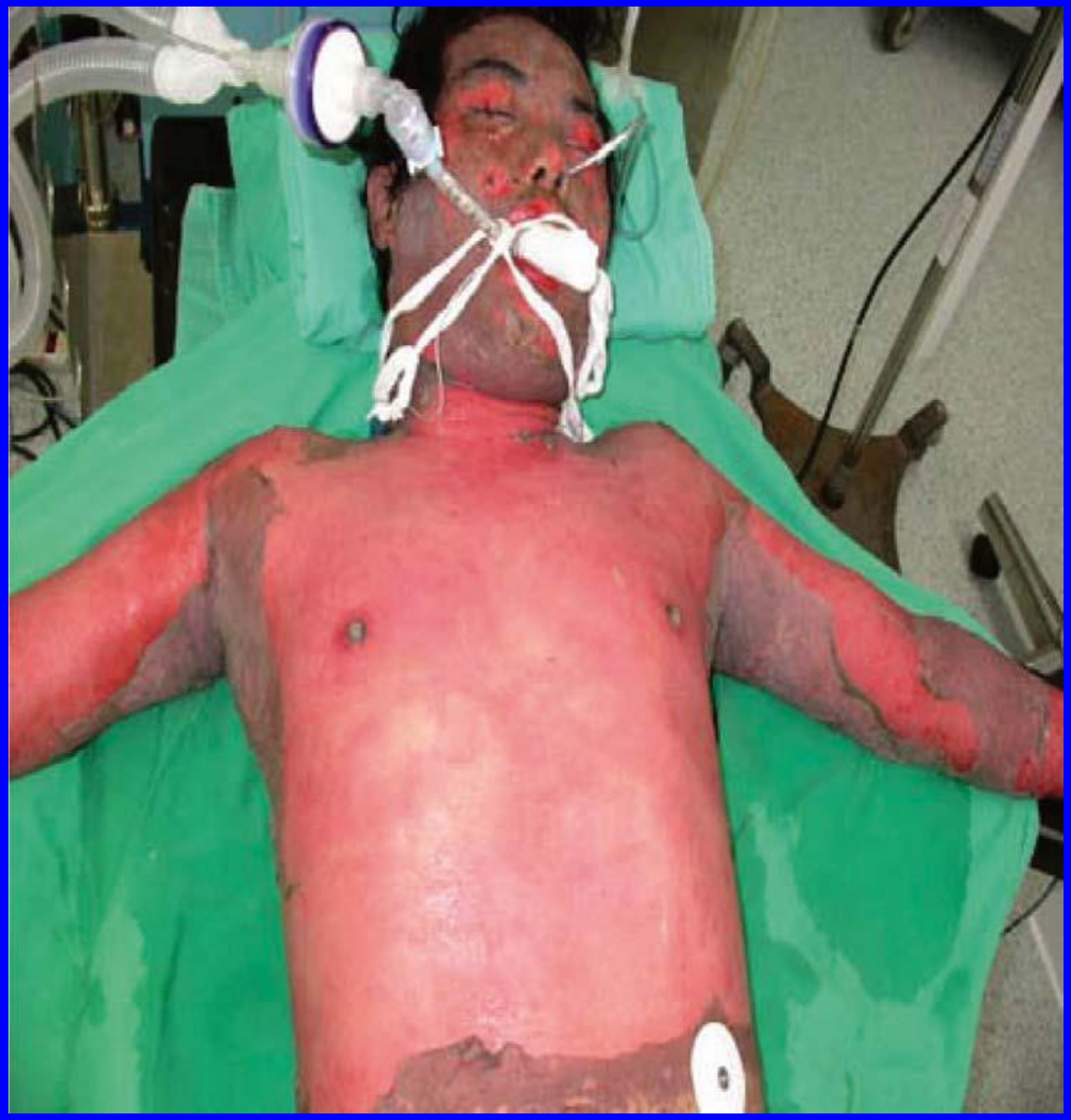


1.1.2.4. Pictures:
Fatal Toxic Epidermal Necrolysis

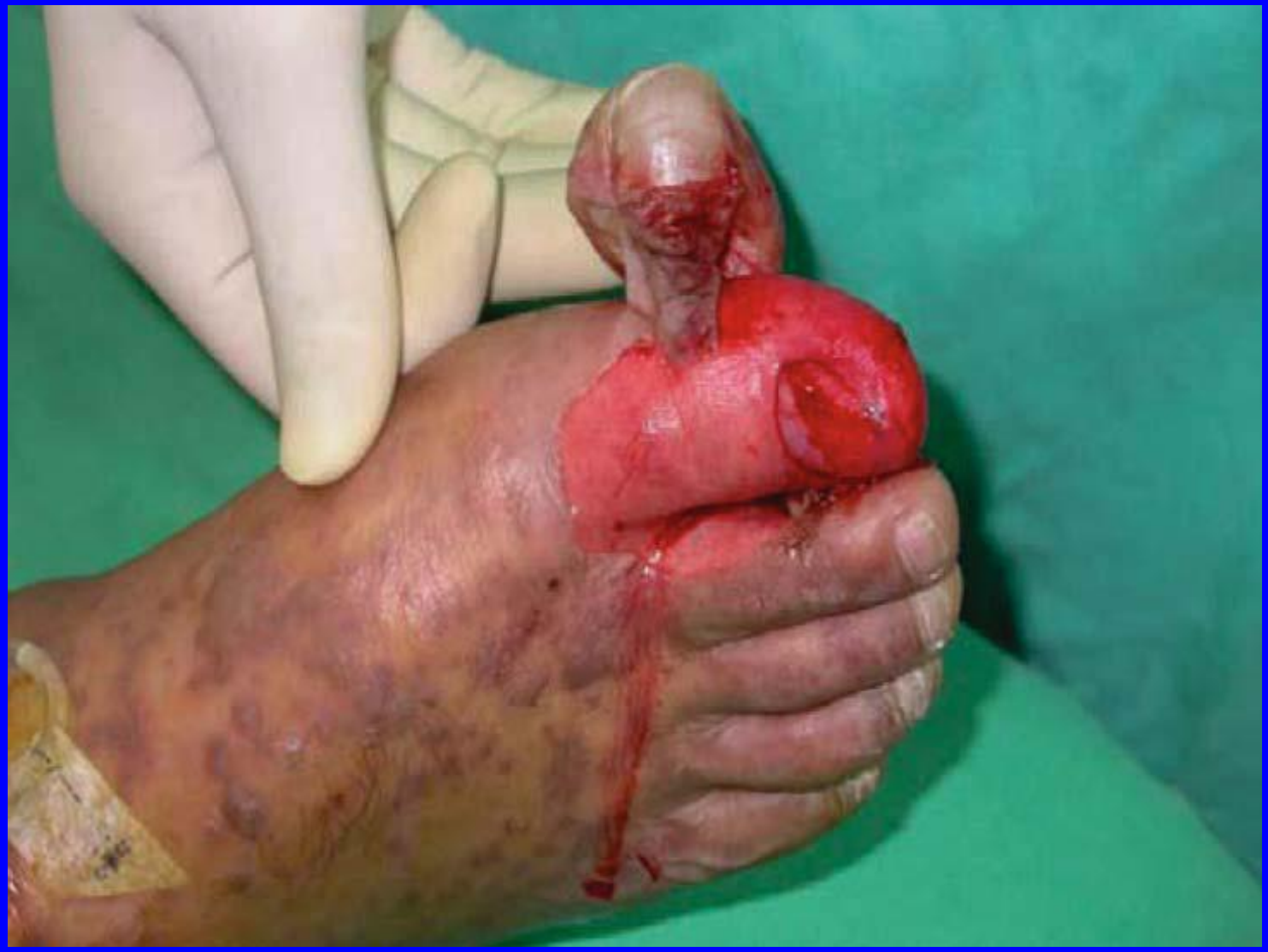
1.1.2.4. Lamotrigine Case 1: Fatal Toxic Epidermal Necrolysis

- A free article is available on PubMed.
  http://www.ncbi.nlm.nih.gov/pubmed/18194909
- It describes a case of Fatal Toxic Epidermal Necrolysis in a Chinese ♂ (Taiwan) on carbamazepine. Remember, almost all of these cases in Chinese can be prevented by HLA-B*15:02 genotyping (see the presentation on “Pharmacogenetic Testing in Psychiatry”).

1.1.2.4. Lamotrigine Case 1: Toxic Epidermal Necrolysis: >90% Skin Detachment



1.1.2.4. Lamotrigine Case 1: Toxic Epidermal Necrolysis: Nail Detachment



1.1.2.5. More Web Pictures

1.1.2.5. Lamotrigine Case 1: More Web Pictures

- If you want to see more pictures, they are available on a support group webpage.
  http://www.sjsupport.org/htmldata/reactionphoto_1.html

1.2. Rechallenge After Rash

1.2. Lamotrigine Case 1: Rechallenge after Rash

- If you are considering a rechallenge after lamotrigine-induced rash, carefully review a free PubMed article. http://www.ncbi.nlm.nih.gov/pubmed/20532155
  - After reviewing the literature, which has a scale for rechallenge risk (not validated but looks helpful to Dr. de Leon),
  - Consult
    - a dermatologist, or
    - primary care physician.

1.3. Lamotrigine Case 1

1.3. Lamotrigine Case 1

1.3.1. Case Description
1.3.2. Medications
1.3.3. Outcome
1.3.4. Interpretation

1.3.1. Case Description

1.3.1. Lamotrigine Case 1: Description

http://www.ncbi.nlm.nih.gov/pubmed/17430308

- 35 yo Caucasian ♀ with bipolar II disorder:
  - also treated for
    - hypothyroidism,
    - gastritis,
    - migraines and
    - asthma
  - voluntary admission to a psychiatric hospital due to a depressed episode with mood-congruent psychotic features

1.3.2. Case Medications

1.3.2. Lamotrigine Case 1: Medications

- On admission she was taking:
  - oxcarbazepine (600 mg/day)
  - topiramate (350 mg/day)
  - fluoxetine (60 mg/day)
  - aripiprazole (15 mg/day)
  - quetiapine (200 mg/day)
  - lithium carbonate (900 mg/day)
  - naproxen (1000 mg/day)
  - pantoprazole (40 mg/day)
  - amoxicillin (1500 mg/day)
  - levothyroxine (50 mcg/day)

1.3.2. Lamotrigine Case 1: Medications

- Oxcarbazepine:
  - was decreased and
  - stopped completely on day 5.
- Lamotrigine ↑ (TOO FAST):
  - started at 50 mg/day on day 2
  - reached 200 mg/day on day 6

1.3.2. Lamotrigine Case 1: Medications

- The patient was discharged on day 8 on:
  - lamotrigine (200 mg/day)
  - topiramate (300 mg/day)
  - aripiprazole (15 mg/day)
  - escitalopram (20 mg/day)
  - naproxen (1000 mg/day)
  - pantoprazole (40 mg/day)
  - levothyroxine (75 mcg/day)
  - hydroxyzine (50 mg/day)
- Lamotrigine titration was very fast but there was no sign of any problem.

1.3.3. Case Outcome

1.3.3. Lamotrigine Case 1: Outcome

- Outside the hospital she was doing well >1 month.
- She developed ulcers on her tongue:
  - on day 42 after the first day of admission
  - 41 days after starting lamotrigine
  - 37 days after being on 200 mg/day of lamotrigine
  - 39 days after stopping oxcarbazepine.
- An outpatient psychiatrist saw oral ulcers suggestive of initial Stevens-Johnson Syndrome:
  - 3 days later
  - on the 45th day after the first day of admission.

  She stopped lamotrigine.

1.3.3. Lamotrigine Case 1: Outcome

http://www.ncbi.nlm.nih.gov/pubmed/17430308

1.3.4. Case Interpretation

1.3.4. Lamotrigine Case 1: Interpretation

- Carbamazepine:
  - is a inducer of lamotrigine metabolism.
  - Its discontinuation will be associated with a slow ↑ lamotrigine serum concentration.
- A case of a serious rash with lamotrigine after carbamazepine was discontinued has been published. http://www.ncbi.nlm.nih.gov/pubmed/15766317

1.3.4. Lamotrigine Case 1: Interpretation

- The hypothesis of this case is that
  - oxcarbazepine behaved as an inducer of lamotrigine metabolism, and
  - its discontinuation was associated with a slow ↑ in lamotrigine serum Cs and, after 2 months, with initial signs of Stevens-Johnson Syndrome.
- Another case of oral ulcers after oxcarbazepine discontinuation in a lamotrigine patient was published with this case. See the presentation on “Lamotrigine Case 2: Drug-Drug Interaction”.

1.3.4. Lamotrigine Case 1: Interpretation

Is oxcarbazepine an inducer of lamotrigine metabolism?

1.3.4. Lamotrigine Case 1: Interpretation

Is oxcarbazepine an inducer of lamotrigine metabolism?

It depends on whom you ask.

1.3.4. Lamotrigine Case 1: Interpretation

- The prescribing information describes oxcarbazepine:
  - can inhibit CYP2C19
  - can induce CYP3A4/5
  - is a weak inducer of UGT:

    "In vitro, the UDP-glucuronyl transferase level was increased, indicating induction of this enzyme. Increases of 22% with MHD and 47% with oxcarbazepine were observed. As MHD, the predominant plasma substrate, is only a weak inducer of UDP-glucuronyl transferase, it is unlikely to have an effect on drugs that are mainly eliminated by conjugation through UDP-glucuronyl transferase (e.g., valproic acid, lamotrigine)."

http://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=OXCARBAZEPINE&pagesize=20&page=1&vfile

1.3.4. Lamotrigine Case 1: Interpretation

- A control study in healthy ♂ subjects performed by lamotrigine marketer: http://www.ncbi.nlm.nih.gov/pubmed/16052246
  - placebo vs.
  - lamotrigine, up to 200 mg/day (days 36-42)

  From day 43 to 53 they were randomized to:
  - placebo
  - oxcarbazepine, up to 1200 mg/day

Oxcarbazepine had no effects on lamotrigine pharmacokinetics, but only 6 days of up to 1200 mg/day of oxcarbazepine were included. 6 days is not enough to see inductive effects.

1.3.4. Lamotrigine Case 1: Interpretation

- Two naturalistic studies reflecting long-term dosing indicate that oxcarbazepine may be a mild lamotrigine inducer (requires 1.2-1.3 x lamotrigine dose).
  http://www.ncbi.nlm.nih.gov/pubmed/10217337
  http://www.ncbi.nlm.nih.gov/pubmed/16157751
- Dr. de Leon believes that oxcarbazepine is a mild inducer, particularly in doses ≥ 1,200 mg/day.
  Mild inducers take weeks/months for:
  - maximal induction or de-induction.

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

1.3.4. Lamotrigine Case 1: Interpretation

- Assuming:
  - oxcarbazepine may be a lamotrigine inducer and
  - that it takes several weeks to see the effects of discontinuation on serum lamotrigine concentration;
- in this patient:
  - lamotrigine 200 mg/day: well-tolerated for 37 days
  - oral ulcers appear > 5 weeks (39 days) after oxcarbazepine was discontinued.
    This suggests that serum lamotrigine concentration ↑ very slowly as the inductive effects of oxcarbazepine disappeared.
  - Lamotrigine titration was fast but it is not clear how that can lead to oral ulcers 37 days after last dose ↑.

1.3.4. Lamotrigine Case 1: Interpretation

- If you doubt that this case can be explained by loss of oxcarbazepine inductive effects on lamotrigine:
  - Please review Lamotrigine Case 2.
    Know that the role of oxcarbazepine was hypothesized as an explanation after reviewing the medications of both patients.
  - Remember that the same outpatient psychiatrist identified these two patients, who:
    - were discharged from the same psychiatric hospital.
    - developed oral ulcers many weeks after discharge and initiation of lamotrigine treatment.
- Psychiatrists may easily miss similar cases.
  A psychiatrist assessing lamotrigine ADRs may not pay attention to a medication discontinued weeks before (>5 weeks after oxcarbazepine discontinuation in this case).

Questions

- Please review the 10 questions on the pdf entitled "Questions on the Presentation – Lamotrigine Case 1: Stevens Johnson Syndrome".
- 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. A
5. B
6. D
7. B
8. A
9. A
10. D