# TRAINING PSYCHIATRISTS TO THINK LIKE PHARMACOLOGISTS: INTRODUCTION (2015 version)

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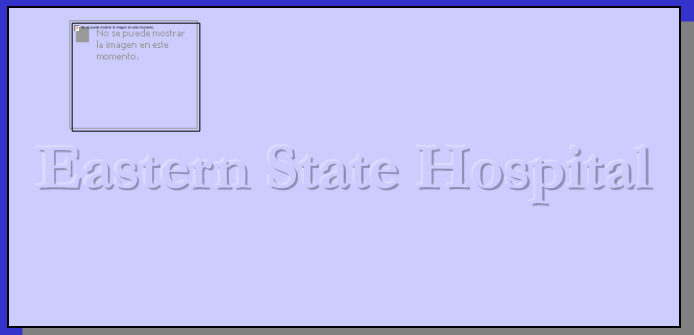

# Clarifications about Web Links

- This set of PowerPoint presentations includes web links.
- Practice with this link to one of Dr. de Leon's article abstracts in PubMed.

  http://www.ncbi.nlm.nih.gov/pubmed/26000191

# Clarifications about Article Downloading

- Most of these PowerPoint presentations summarize previously published articles.
- The presentations have links to download the articles. Dr. de Leon may provide two links:
  - PubMed: some of the articles are offered for free there. http://www.ncbi.nlm.nih.gov/pubmed/26000191
  - Dr. de Leon has started the process of placing pdfs of published articles or at least the final text version before publication on his university page: http://uknowledge.uky.edu/psychiatry_facpub/3/
- If you use Research Gate, you will find some of his articles there, too:

https://www.researchgate.net/publication/276133566_Three_Patients_Needing_High_Doses_of_Valproic_Acid_to_Get_Therapeutic_Concentrations

# Contents of this Introduction

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# Contents of this Introduction

# 1. Dr. de Leon's Limitations

# 1. Dr. de Leon's Limitations

1.1. Conflicts of Interest

1.2. Biases

1.3. Personal Limitations

# 1.1. Conflicts of Interest

# 1.1. Conflicts of Interest: Current

1) In the past 3 years, Dr. de Leon had no conflicts of interest.
2) No commercial company had any role or influence in writing these presentations.
3) He has never lectured using pharmaceutical companies' slides. He has no stocks and has never been a consultant for pharmacogenetics or pharmaceutical companies.
4) He has no commercial relations with authors or publishers of the books or articles listed in these presentations. He expects no personal benefits from listing Amazon web-page book links. Dr. de Leon is NOT recommending that you use Amazon to buy these books. Amazon is a convenient way to identify books.

# 1.1. Conflicts of Interest: Past

1) Dr. de Leon has received researcher-initiated grants from Eli Lilly (one ended in 2003 and the other, as co-investigator, ended in 2007), from Roche Molecular Systems, Inc. (ended in 2007), and in a collaboration with Genomas, Inc., from the NIH Small Business Innovation Research program (ended in 2010).
2) He was on the advisory boards of Bristol-Myers Squibb (2003/04) and AstraZeneca (2003).
3) Roche Molecular Systems supported one of his educational presentations, which was published in a peer-reviewed journal (2005).
4) His lectures have been supported once by Sandoz (1997), twice by Lundbeck (1999 and 1999), twice by Pfizer (2001 and 2001), 3 times by Eli Lilly (2003, 2006, and 2006), twice by Janssen (2000 and 2006), once by Bristol-Myers Squibb (2006), and 7 times by Roche Molecular Systems, Inc. (once in 2005 and 6 times in 2006).

# 1.2. Biases

# 1.2. Biases

- Dr. de Leon believes that the psychopharmacology literature and psychopharmacology education has been biased by pharmaceutical companies.
- The US outcome has been paradoxical:
  - undertreatment of the severely mentally ill, and
  - overtreatment of minor psychiatric problems.

http://uknowledge.uky.edu/psychiatry_facpub/25/

http://www.ncbi.nlm.nih.gov/pubmed/24781438

# 1.2. Biases

- Dr. de Leon reviews deaths of psychiatric patients in the Kentucky public system.
- He believes that psychiatric drugs are potentially toxic (and some can be abused).
- If a clinician decides to use any of them to treat a patient, he/she needs to complete a careful risk/benefit analysis and monitor toxicity very closely.

# 1.3. Personal Limitations

# 1.3. Personal Limitations: His Training

- Dr. de Leon is a physician by training. As with all physicians, he had relatively weak pharmacology training during medical school. During his 4-year fellowship in clinical psychopharmacology he was mentored by a psychiatrist.
- He has the "fantasy" that he can train himself by unsupervised reading; thus he has "tried" to train himself in
  - statistics,
  - pharmacology and, more recently, in
  - philosophy.

## 1.3. Personal Limitations: Pharmacological Training

- During the last 20 years Dr. de Leon's extensive reading in pharmacology was necessitated by his need to treat or consult on difficult patients.
- He has collaborated in pharmacological research with pharmacists and clinical pharmacologists.
- His pharmacological reading has proven useful since he has published in pharmacological and pharmacogenetics journals. Moreover, he reviews articles for many of them.
- These presentations approach pharmacology using pharmacokinetic and pharmacodynamic mechanisms. Pharmacokinetic mechanisms are usually neglected in psychiatric textbooks.

## 1.3. Personal Limitations: Clinical Practice

- Dr. de Leon has
  - expertise in antipsychotics and mood stabilizers,
  - some expertise in other psychiatric drugs, and
  - limited expertise in non-psychiatric drugs.
- Dr. de Leon has reviewed and discussed all the non-psychiatric drugs in every presented case in these PowerPoint presentations. All drugs may be important when considering pharmacological response.

# 1.3. Personal Limitations: Opinion

- Dr. de Leon cannot deny that these presentations are based on:
  - limited evidence, and
  - Dr. de Leon's personal interpretation of the literature. In summary, his "opinions".
- If one defends the position of
  - many pharmaceutical companies, one can argue that these presentations exaggerate the potential for drug-drug interactions.
  - many pharmacogenetics companies, one can argue that these presentations may jeopardize the potential of pharmacogenetic testing in psychiatry.

# 1.3. Personal Limitations: Opinion

- Some pharmacologists better trained than him and highly regarded in the literature have questioned one of Dr. de Leon's ideas:
  - Valproate can be an inducer in some situations (it is traditionally considered an inhibitor of the metabolism of some drugs).
- Some journal reviewers (they appeared to be practicing epileptologists) have questioned Dr. de Leon's recommendation that, very rarely, a patient taking antiepileptic inducers may need to be prescribed extremely high doses of psychiatric drugs until the drug levels are therapeutic.
- Time will tell how "wrong" these ideas are.

# 2. Course

# 2. Course

2.1. Course Description
2.2. Educational Objectives
2.3. Course Limitations
2.4. Future Plans

# 2.1. Course Description

# 2.1. Course Description

This course attempts to teach psychiatrists to think in pharmacological terms and to use pharmacological principles to improve the treatment of their patients. Many presentations are practical, as they are based on real cases.

# 2.1. Course Description: Components

This course has two sections:

1. Basic principles in clinical pharmacology: theoretical lectures that may be boring.
2. Cases: In this section pharmacological principles are applied to interpret cases. Most cases are from Dr. de Leon's practice, usually after publication in peer-reviewed journals. Rarely, Dr. de Leon includes particularly educative cases from the published literature.

# 2.1. Course Description

2.1.1. Theoretical Lectures

2.1.2. Cases

# 2.1. Course Description

- 32 lectures:
  - 14 theoretical lectures:
    each with a set of 10 questions
  - 18 case presentations:
    each with a set of 10 questions

# 2.1.1. Theoretical Lectures

# 2.1.1. Theoretical Lectures

- 5 on general concepts
- 9 on drug classes

## 2.1.1. Theoretical Lectures

2.1.1.1. Theoretical Lectures on General Concepts

2.1.1.2. Theoretical Lectures on on Drug Classes

# 2.1.1.1. Theoretical Lectures on General Concepts

## 2.1.1.1. Five Theoretical Lectures on General Concepts

- Introduction to Clinical Pharmacology
- Introduction to Statistical Concepts Needed for Clinical Pharmacology
- Personalized Medicine in Psychiatry
- Evidence-Based Medicine vs. Personalized Medicine
- Pharmacogenetic Testing in Psychiatry

# 2.1.1.2. Theoretical Lectures on Drug Classes

# 2.1.1.2. Nine Theoretical Lectures on Drug Classes

- Pharmacokinetics of Antidepressants
- Pharmacodynamics of Antidepressants
- Pharmacokinetics of Oral Second-Generation Antipsychotics
- Pharmacodynamics of Second-Generation Antipsychotics
- Pharmacokinetics of Lithium
- Pharmacokinetics of Lithium
- Induction by Antiepileptic Drugs: An Introduction for Clinicians
- Pharmacokinetics of Antiepileptic Drugs
- Pharmacodynamics of Antiepileptic Drugs

# 2.1.2. Case Presentations

## 2.1.2. Eighteen Case Presentations

2.1.2.1. Six Cases on Clozapine
2.1.2.2. Two Cases on Risperidone
2.1.2.3. Three Cases on Quetiapine
2.1.2.4. Two Cases on Lamotrigine
2.1.2.5. Three Cases on Valproate
2.1.2.6. Two Other Cases

# 2.1.2.1. Six Clozapine Case Presentations

- Clozapine Case 1: CYP Relevance
- Clozapine Case 2: Infection
- Clozapine Case 3: Sertraline
- Clozapine Case 4: Perphenazine
- Clozapine Case 5: High Dose
- Clozapine Case 6: Half Life

# 2.1.2.2. Two Risperidone Case Presentations

- Risperidone Case 1: Drug-Drug Interaction
- Risperidone Case 2: Genetics

# 2.1.2.3. Three Quetiapine Case Presentations

- Quetiapine Case 1: Warfarin
- Quetiapine Case 2: Concentrations
- Quetiapine Case 3: Akathisia

# 2.1.2.4. Two Lamotrigine Case Presentations

- Lamotrigine Case 1: Stevens Johnson Syndrome 1
- Lamotrigine Case 2: Stevens Johnson Syndrome 2

# 2.1.2.5. Three Valproate Case Presentations

- Valproate Case 1: Pharmacokinetics
- Valproate Case 2: Safety
- Valproate Case 3: Formulations

# 2.1.2.6. Two Other Case Presentations

- One Case on Death on Antipsychotics
- One Case of Acute Dystonic Reaction

# 2.2. Educational Objectives

# 2.2. Educational Objectives

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

1. Show familiarity with clinical pharmacology concepts, including pharmacokinetics, pharmacodynamics, drug efficacy and safety.

2. Understand how these principles can be applied to specific individual cases.

3. Hopefully start applying them to the treatment of his/her patients using the appropriate literature.

# 2.2. Educational Objectives and Questions

At the conclusion of each presentation (except this introduction), the participant should answer 10 questions:

1. The questions are simple and focus on crucial issues.
2. There is no intent to trick the reader.
3. If the reader misses a question, he/she may review the presentation to reinforce the concepts.
4. Grasping the pharmacological concepts in one presentation is necessary for understanding the succeeding presentations. The reading order of the lectures may vary according to the tastes/training of the reader.

# 2.3. Course Limitations

# 2.3. Course Limitations

- As Dr. de Leon has no formal training in pharmacology, it is possible that in the process of explaining pharmacological concepts to make them understandable to clinicians, he has oversimplified too much. To combat this problem, he provides references that can be checked by readers.
- Similarly, as Dr. de Leon has no formal training in statistics, it is possible that on rare occasions when he jumps into the troubled waters of statistics and tries explaining statistical concepts to make them understandable to clinicians, he has oversimplified too much. To combat this problem, he provides references that can be checked by readers.

# 2.3. Course Limitations

- The practical aspect of interpreting cases is more an art than a science.
- Four arguments support the strength of Dr. de Leon's interpretations:
  - Dr. de Leon has published >30 case reports in peer-reviewed journals.
  - Almost all cases presented in this course have been published in peer-reviewed journals.
  - Dr. de Leon is frequently asked to review for publication case reports in psychiatric journals (e.g. *Am J Psychiatry, J Clin Psychopharmacol…*)
  - Some of these cases have so much repeated information that it can be analyzed with statistical methods.

# 2.4. Future Plans

# 2.4. Future Plans

- This 2015 version does not cover every aspects of psychopharmacology. It is merely an attempt to start to make these presentations widely available.

- If the course is successful, every year the course will be improved by:
  - updating prior presentations, and
  - adding new ones.

# 3. Your Limitations

# 3. Your Limitations

- This PowerPoint presentation was originally developed to teach psychiatry residents.
- The next section focuses on physicians' limitations.
  They may not apply to other clinicians, including:
  - pharmacy students and pharmacists:
    In Dr. de Leon's experience in the US, pharmacists have an easier time following the presentations and thinking using pharmacokinetic and pharmacodynamic mechanisms.
  - other clinicians:
    Their ability to follow the presentations depends on their pharmacological knowledge.

# 3. Your Limitations

3.1. Physician's Limitations

3.2. Limitations of Clinical Knowledge

3.3. Reflections on an Alternative Title

# 3.1. Physician's Limitations

# 3.1. Physician's Limitations

3.1.1. Limitations in Thinking

3.1.2. Limitations in Access to Knowledge

3.1.3. Limitations in the Use of Knowledge

# 3.1.1. Physician's Limitations in Thinking

# 3.1.1. Physicians' Limitations in Thinking

- In the last 10 years there has been interest in how doctors think. There is a realization that, as part of their medical training, physicians have learned to ignore their thinking process, so few physicians are able to learn from their mistakes. Jerome Groopman, M.D., a Harvard professor, has written a very entertaining book: Groopman, Jerome (2006). *How Doctors Think*. Boston: Mariner Books. http://www.amazon.com/How-Doctors-Think-Jerome-Groopman/dp/B0029LHWKY/ref=sr_1_1?ie=UTF8&s=books&qid=1279046717&sr=1-1 He states, "My generation was never explicitly taught how to think as clinicians. We learned medicine catch-as-catch-can. Trainees observed senior physicians the way apprentices observed master craftsmen in a medieval guild, and somehow the novices were supposed to assimilate their elders' approach to diagnosis and treatment. Rarely did an attending physician actually explain the mental steps that led him to his decisions."

# 3.1.1. Physicians' Limitations in Thinking

- This is not a new idea. Michael Polanyi was a Hungarian who started as a physician, moved to chemist researcher and then to philosopher. He created the concept of "tacit knowledge". He proposed that "tacit knowledge" is learned by practicing as an apprentice under a teacher, and that it cannot be completely articulated in words but taught by example. Goldman summarizes these ideas in this free article: http://www.ncbi.nlm.nih.gov/pubmed/2356625

# 3.1.2. Physician's Limitations in Access to Knowledge

## 3.1.2. Physicians' Limitations in Access to Knowledge

- Pharmacology teaching in medical school: limited.
- Psychiatric textbooks and journals pay attention to some aspects of clinical pharmacology but other aspects (particularly pharmacokinetics) are usually ignored.
- Clinical pharmacology journals are read by PhDs and pharmacists. Psychiatrists rarely read them.
- Drug prescribing informations (or package inserts) are rarely read by psychiatrists. In the U.S. they are available http://dailymed.nlm.nih.gov/dailymed/about.cfm on DailyMed. Those approved >10 years ago tend be of poor quality and neglect the area of drug-drug interactions. http://www.ncbi.nlm.nih.gov/pubmed/21508855

# 3.1.3. Physician's Limitations in the Use of Knowledge

## 3.1.3. Physician's Limitations in the Use of Knowledge

- Blood levels, called therapeutic drug monitoring (TDM) by pharmacologists, can be used to personalize dosing.
- Psychiatrists can get confused by them unless they collect TDM taking into account:
  - steady state and half lives (see Clozapine Case 6), and
  - drug-drug interactions.
- The only way that Dr. de Leon knows how to teach the practical use of TDM is through:
  - the case reports included in this course,
  - which use the concept of concentration/dose ratio.

# 3.2. Limitations of Clinical Knowledge

## 3.2. Limitations of Clinical Knowledge

3.2.1. In General

3.2.2. In Psychopharmacology

# 3.2.1. Limitations of Clinical Knowledge in General

# 3.2.1. General Limitations in Clinical Knowledge

- According to Naylor (1995):

"Clinical medicine seems to consist of

- a few things we know,
- a few things we think we know (but probably don't), and
- lots of things we don't know at all."

http://www.ncbi.nlm.nih.gov/pubmed/7898234

# 3.2.2. Limitations of Clinical Knowledge in Psychopharmacology

## 3.2.2. Limitations of Clinical Knowledge in Psychopharmacology

3.2.2.1. Teaching by Pharmaceutical Companies
3.2.2.2. Teaching on Pharmacogenetic Tests
3.2.2.3. Teaching on Drug-Drug Interactions

# 3.3.2.1. Teaching by Pharmaceutical Companies

## 3.3.2.1. Teaching by Pharmaceutical Companies

- Training regarding new drugs is mainly left in the "biased" hands of pharmaceutical companies.

- The pharmaceutical company's main goal is to sell their drugs, not to train good physicians.

# 3.3.2.2. Teaching on Pharmacogenetic Testing

## 3.3.2.2. Teaching on Pharmacogenetic Testing

- Many companies are marketing pharmacogenetic tests for psychiatric patients in the US and other Western countries.
- Test approval is not well-regulated and there is no need to demonstrate clinical utility.
- The pharmacogenetic company's main goal is to sell their tests.

# 3.3.2.2. Teaching on Pharmacogenetic Testing

- An article (http://uknowledge.uky.edu/psychiatry_facpub/27/ http://www.ncbi.nlm.nih.gov/pubmed/25200585) and a lecture from this course propose a limited role for pharmacogenetic tests in psychiatry.

# 3.3.2.3. Teaching on Drug-Drug Interactions

# 3.3.2.3. Teaching on Drug-Drug Interactions

- Dr. de Leon does not know a "single" good literature source for all drug-drug interactions.
  - Computer programs
    - tend to be overinclusive
    - do not pay attention to clinical relevance
    - are frequently ignored by busy clinicians
  - Books are outdated when finally published.
  - Prescribing information (package inserts) frequently includes studies designed to be negative.

# 3.3.2.3. Teaching on Drug-Drug Interactions

- Dr. de Leon develops his own review articles based on:
  - pharmacological studies: very limited
  - published case reports, and
  - extrapolation from pharmacological mechanisms.
- Dr. de Leon believes the psychiatric literature does not pay enough attention to:
  - Inhibitory effects of some antidepressants
  - Inductive effects of some antiepileptic drugs used in psychiatry as mood stabilizers.

  He wrote an editorial on the contamination of the literature by false negative findings in:
    - epilepsy: http://uknowledge.uky.edu/psychiatry_facpub/23/
    - bipolar disorder: http://uknowledge.uky.edu/psychiatry_facpub/24/

# 3.3.2.3. Teaching on Drug-Drug Interactions

- Dr. de Leon's approach is not strictly an evidence-based medicine approach:
  - Evidence is contaminated by false negative findings.
  - Studies focused on averages do not represent outliers (see the lecture on evidence-based medicine).
  - He is not supported by the deep pockets of the pharmaceutical companies. He has no funding for the needed studies using clinically-relevant doses of inhibitors and inducers for each psychiatric drug.
- Dr. de Leon's approach is based on some knowledge:
  - Pharmacodynamic mechanisms of safety are reasonably well-understood in psychiatry.
  - Pharmacokinetic mechanisms are easy to understand:
    - Adding an inducer is equivalent to ↓ the dose of a substrate.
    - Adding an inhibitor is equivalent to ↑ the dose of a substrate.

  Using this perspective, their clinical relevance depends on how relevant you consider the change in dosage.

# 3.3.2.3. Teaching on Drug-Drug Interactions

- Regarding drug-drug interactions in psychiatry, Dr. de Leon sees two possible positions:
  - Conservative and easy:
    you are willing to wait 10 years until better evidence is available.
    - Dr. de Leon suggests that if you believe in prayer, you pray that nothing happens to your patients.
    - Dr. de Leon has seen deaths caused by psychiatric medications, frequently in situations of polypharmacy.
  - Uncompromising and difficult:
    You try to learn about drug-drug interactions using:
      - pharmacokinetic mechanisms, and
      - pharmacodynamic mechanisms.

# 3.3.2.3. Teaching on Drug-Drug Interactions

- Best way of learning drug-drug interactions:
  Review all presentations: they are most updated
  Several Case Presentations are focused
  on drug-drug interactions

- The next two slides provide links of tables/figures summarizing this approach.
  In the future Dr. de Leon will try to place them in a single location.

# 3.3.2.3. Teaching on Drug-Drug Interactions

- Summaries of:
  - pharmacokinetics of second-generation antipsychotics:

    Table 2 http://uknowledge.uky.edu/psychiatry_facpub/42/
  - pharmacodynamics of second-generation antipsychotics:

    Figures 3 and 4 http://uknowledge.uky.edu/psychiatry_facpub/42/
  - pharmacokinetics of antiepileptic drugs

    Table 1 and Figure 1 http://uknowledge.uky.edu/psychiatry_facpub/40/
  - pharmacodynamics of antiepileptic drugs

    Figures 2 and 3 http://uknowledge.uky.edu/psychiatry_facpub/40/
  - pharmacokinetics of antidepressants

    Table 2 http://uknowledge.uky.edu/psychiatry_facpub/40/
  - pharmacodynamics of antidepressants

    Figures 4 and 5 http://uknowledge.uky.edu/psychiatry_facpub/40/

# 3.3.2.3. Teaching on Drug-Drug Interactions

- Summaries of drug-drug interactions with possible practical relevance:
  - Antiepileptics & second-generation antipsychotics:

    Table 5 http://uknowledge.uky.edu/psychiatry_facpub/39/
  - Antidepressants & second-generation antipsychotics:

    Table 4 http://uknowledge.uky.edu/psychiatry_facpub/42/
  - Antiepileptics & antidepressants:

    Table 4 http://uknowledge.uky.edu/psychiatry_facpub/40/

# 3.3. Reflections on an Alternative Title

# Alternative Title:
# TRAINING DOGS HOW TO THINK LIKE CATS

# 3.3. Reflections on an Alternative Title

Be aware that if you are a **dog**
(a psychiatrist trained in the "usual way"),

you will have a hard time
learning how to think like a **cat**
(a psychiatrist who uses
pharmacological principles).

# 3.3. Reflections on an Alternative Title

1. If you think that you know everything about prescribing psychiatric drugs, you will not benefit from this course.

2. If you are not willing to question your prescription “habits”, you cannot change them.

3. Psychopharmacology, like any area of medicine, changes rapidly. If you do not develop a system for updating your pharmacological knowledge, it will become obsolete in a few years.

# 3.3. Reflections on an Alternative Title

- Do you have a system for continuously updating your training?
- If you do not have one (and are not planning to develop one) this course may not be helpful to you.
- If you do not update your pharmacological training, you may need to consider stopping your prescribing of psychiatric medications.

*Thank you*