Personalized Medicine in Psychiatry

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(3-11-16)

Most sections of this lecture are based on an article:

"Focusing on Drug versus Disease Mechanisms and on Clinical Subgrouping to Advance Personalised Medicine in Psychiatry.
Acta Neuropsychiatr 2014;26:327-33"

http://www.ncbi.nlm.nih.gov/pubmed/25455256

Pre-published free version:

http://uknowledge.uky.edu/psychiatry_facpub/29

Other used articles are described
in the corresponding section and the reference list.

Learning Objectives

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

1) Understand the difficulties of using disease biomarkers in psychiatry for implementing personalized medicine in psychiatry.
2) Appreciate the relevance of pharmacological mechanisms for the implementation of personalized medicine in psychiatry.
3) Remember that clinical subgrouping has been used for implementing personalized medicine in psychiatry.

Abbreviations

- ADR: adverse drug reaction
- APA: American Psychiatric Association
- CSF: cerebrospinal fluid
- CYP: cytochrome P450
- DDI: drug-drug interaction
- DST: dexamethasone suppression test
- EBM: evidence-based medicine
- FDA: Food & Drug Administration
- NCI: National Cancer Institute: cancer research program funded by the US federal government
- NIMH: National Institute of Mental Health: psychiatric research program funded by the US federal government
- RCT: randomized clinical trial
- TCA: tricyclic antidepressant
- TDM: therapeutic drug monitoring
- UGT: uridine diphosphate glucuronosyltransferase
- UM: ultrarapid metabolizer

Definitions

- Many articles consider Pharmacogenetic Testing to be the same as Pharmacogenomic Testing.
- Some articles distinguish:
  - Pharmacogenetic Testing: 1 gene
  - Pharmacogenomic Testing: multiple genes at the same time

Lecture Content

0. Personalized Prescription

1. Disease Mechanisms for Personalizing Prescription

2. Drug Mechanisms for Personalizing Prescription

3. Clinical Subgrouping for Personalized Prescription

4. Conclusions

Lecture Content

0. Personalized Medicine

0. Personalized Medicine

0.1. At First Glance: An Easy Concept

0.2. Upon Further Review: A Complex Concept

0.1. Personalized Medicine. At First Glance: An Easy Concept

0.1. Personalized Medicine: An Easy Concept

- At first glance, personalized medicine is a concept easy to understand:
  - All physicians have experienced that "Every patient is different."
- If this is correct, there is need for **Personalized Medicine.**

0.1. Personalized Medicine: An Easy Concept

- Personalized Medicine can be expressed as:
  - Personalized Surgery
  - Personalized Rehabilitation
  - Personalized Nutrition
  - Personalized Prescription = the application of the concept of personalized medicine to the prescription of drugs.

0.1. Personalized Medicine: An Easy Concept

- Pharmaceutical companies approve drugs for an average individual who should receive average doses.
  Not all individuals are average nor do they respond in an average way.
- For more details on statistical issues regarding the representativeness of means, see the presentation “Evidence-Based Medicine versus Personalized Medicine: Are They Enemies?”

0.1. Personalized Medicine: An Easy Concept

- Personalized Medicine can be expressed in psychiatry as:
  - Personalized Prescription (the focus of this lecture)
  - Personalized Electroconvulsive Therapy
  - Personalized Psychotherapy (easiest to personalize)

0.2. Personalized Medicine.
Upon Further Review: A Complex Concept

0.2. Personalized Medicine: A Complex Concept

- In 2004 in the first issue of the newly created journal *Personalized Medicine*, Ruaño, the editor, reminded us that physicians have traditionally practiced personalized medicine in their attempts to decide the best treatment for each of their patients.

  "Medicine has always been personalized. The patient-doctor relationship, both extolled and beleaguered, has historical aspirations and cultural roots in healing each person."

  www.futuremedicine.com/doi/pdf/10.1517/17410541.1.1.1

0.2. Personalized Medicine: A Complex Concept

- The traditional approach:
  - Physicians were not using the term "personalized medicine".
  - was probably based on subjective physician preferences and not on scientific knowledge.
- A key element in the definition of personalized medicine is which element you are using to define/separate individuals.

0.2. Personalized Medicine: A Complex Concept

- For example, in a 1952 book by Osborne: *Psychiatry and Medicine: An Introduction to Personalized Medicine*
  - the psychoanalytic tradition is followed.
  - individuals are differentiated by psychoanalytic-based psychological mechanisms.
- In the 1990s, the rise of personalized medicine was based on genetic mechanisms. Each individual has different genes.

0.2. Personalized Medicine: Concept Complexity

- The concept of personalized medicine or, more narrowly, personalized prescription, can be applied in psychiatry using 3 different approaches which have different traditions:
  - disease mechanisms: biomarkers
  - drug mechanisms: pharmacogenetics
  - clinical subgrouping
- The view of personalized medicine embraced by this presentation is much more complex than at first glance would suggest.

1. Disease Mechanisms

1. Disease Mechanisms

1.1. Biological Tests in Psychiatry
1.2. Biomarkers
1.3. The Concept of Disease in Psychiatry

1.1. Biological Tests in Psychiatry

This section is taken from a 2012 article

http://www.ncbi.nlm.nih.gov/pubmed/22367661

Pre-published Version: http://uknowledge.uky.edu/psychiatry_facpub/41/

1.1. Biological Tests in Psychiatry

- Before the current interest in biomarkers in psychiatry, biological psychiatric researchers tried to explore heterogeneity in drug response using biological tests in psychiatry.
- The biological tests targeted disease mechanisms.
- The 2 best examples:
  - serotonergic versus noradrenergic types of depression
  - the DST

1.1. Biological Tests in Psychiatry

1.1.1. Serotonergic vs. Noradrenergic Depression
1.1.2. The DST

1.1.1. Serotonergic vs. Noradrenergic Depression

1.1.1. Serotonergic vs. Noradrenergic Depression

- The monoamine hypothesis of depression was first formulated in the 1960s.

http://www.ncbi.nlm.nih.gov/pubmed/10775017

- Some evidence, particularly CSF studies, http://www.ncbi.nlm.nih.gov/pubmed/4420178 suggested that different first-generation antidepressants had differential effects on serotonin and noradrenalin metabolites.
- This led to efforts to classify depressed patients according to pharmacological mechanisms explaining their depression.

1.1.1. Serotonergic vs. Noradrenergic Depression

- In 1975, Maas hypothesized two groups of depressed patients:
  - A (with disorders of the norepinephrine systems)
  - B (with disorders of the serotonin systems).

http://www.ncbi.nlm.nih.gov/pubmed/1200759

1.1.1. Serotonergic vs. Noradrenergic Depression

- This model was supported by one of the first pharmacological guidelines in psychiatry:

http://www.ncbi.nlm.nih.gov/pubmed/7369397

  - came along in 1980, before the EBM movement
  - was developed by 3 experts
  - used a comprehensive approach including
    - mechanistic approaches,
    - RCTs
  - tried to balance all kinds of data:
    - biological and
    - clinical

1.1.2. The DST

1.1.2. The DST

- The DST (dexamethasone suppression test) has been:
  - the most important biomarker
  - used as a potential index of heterogeneity of treatment response in depression.

1.1.2. The DST

- 1976 DST research studies in depression led to enthusiasm.

http://www.ncbi.nlm.nih.gov/pubmed/962488 http://www.ncbi.nlm.nih.gov/pubmed/962489

- 1987 APA guideline: http://www.ncbi.nlm.nih.gov/pubmed/3310667
  - a lack of definitive data of the DST's clinical usefulness in selecting treatment
- Nierenberg & Feinstein http://www.ncbi.nlm.nih.gov/pubmed/3278149
  - used the history of the DST,
    - a diagnostic test initially widely accepted
    - and later rejected,

as a cautionary example for diagnostic tests.

1.2. Biomarkers

1.2. Biomarkers

- From 2010-2015, psychiatric journals:
  - http://www.ncbi.nlm.nih.gov/pubmed/21646577
  - http://www.ncbi.nlm.nih.gov/pubmed/22050858
  - http://www.ncbi.nlm.nih.gov/pubmed/23968984
  - http://www.ncbi.nlm.nih.gov/pubmed/23680237
  - http://www.ncbi.nlm.nih.gov/pubmed/24562493
  - started discussing personalizing treatments
  - by focusing on disease mechanisms.
- This:
  - may be new in psychiatry,
  - but follows the tradition of “biomarkers”.

1.2. Biomarkers

1.2.1. Biomarkers: Concept
1.2.2. Biomarkers in Oncology: Reality
1.2.3. Biomarkers in Psychiatry: Marketing

1.2.1. Biomarkers: Concept

1.2.1. Biomarkers: Concept

- Technological advances:
  - started with microarrays including DNA,
  - extended to all biological molecules:
    - RNA,
    - proteins,
    - lipid metabolites…
- Leading to diagnostic branches:
  - pharmacogenomics,
  - transcriptomics,
  - proteonomics,
  - metabolonomics…

1.2.1. Biomarkers: Concept

- All of these are called biomarkers and can be used for drug development.
- Biomarkers are defined by Wagner:

"a characteristic that is:

- objectively measured and
- evaluated as an indicator of
  - normal biological processes,
  - pathogenic processes, or
  - pharmacological response(s) to a therapeutic intervention."

http://www.ncbi.nlm.nih.gov/pubmed/12364809

1.2.1. Biomarkers: Concept

- Following Wagner's definition,
  they can be classified as:
  - biomarkers of normal biological processes,
    (not further discussed in this presentation)
  - disease biomarkers
    which reflect disease mechanisms
  - pharmacological biomarkers
    which reflect pharmacological mechanisms
    (see section 2 on drug mechanisms)

1.2.1. Biomarkers: Concept

- Provide millions of pieces of data leading to:
  - a new scientific approach: "Complexity"
  - the introduction of bioinformatics and new types of analyses: "network medicine"

http://www.ncbi.nlm.nih.gov/pubmed/21164525

These concepts are further discussed in the presentation "Evidence-Based Medicine versus Personalized Medicine".

- Personalized medicine using disease biomarkers has become a "fad" in medicine.

1.2.2. Biomarkers in Oncology: Reality

1.2.2. Biomarkers in Oncology

- Personalized medicine using disease biomarkers in oncology is not a “fad”; it is a reality.
- Success in oncology is explained by 2 facts:
  - cancerous tissue is available to:
    - validate the diagnosis and
    - study the disease mechanisms, and
  - knowledge of disease mechanisms at the molecular biology level helps to select individualized treatments.

These facts are absent in psychiatry.

1.2.3. Biomarkers in Psychiatry: Marketing

1.2.3. Biomarkers in Psychiatry

- If you are the director of the NIMH and
  are competing with NCI for funding,
  it is not surprising that you would use marketing:
  - in 2006: you propose to “cure” mental illness
    http://www.ncbi.nlm.nih.gov/pubmed/16355250
  - in 2012: you propose that personalized treatment
    using disease mechanisms
    is the way to do it.

    http://www.ncbi.nlm.nih.gov/pubmed/22869033

1.2.3. Biomarkers in Psychiatry

- If you are Dr. de Leon, who hates marketing and considers it one of the worst traits of US society, you acknowledge that:
  - psychiatry is the specialty in medicine that lags behind in the definition of diseases (*only* 150 years) http://www.ncbi.nlm.nih.gov/pubmed/15914753 and
  - even focusing on "psychiatric diseases", such as Alzheimer disease, is not good news; the complexity of brain mechanisms currently appears insurmountable.

1.3. The Concept of Disease in Psychiatry

1.3. The Concept of Disease in Psychiatry

1.3.1. Jaspers' Classification
1.3.2. Brain Complexity: Alzheimer Disease

1.3.1. The Concept of Disease in Psychiatry: Jaspers' Classification

1.3.1. Jaspers' Concept of Psychiatric Diseases

- Dr. de Leon follows Jaspers' ideas about psychiatric nosology: http://www.ncbi.nlm.nih.gov/pubmed/25849592
- He believes that:
  - schizophrenia,
  - bipolar disorder,
  - severe major depression, and
  - catatonia

  are syndromes.
  They are not "medical diseases".

1.3.1. Jaspers' Concept of Psychiatric Diseases

- Colon cancer:
  - is being divided into different diseases based on pathogenic mechanisms using molecular biology.
- Psychiatry has no way of:
  - validating diagnoses and establishing borders (e.g., we can not separate: ● schizophrenia and ● bipolar disorder using genetics and/or statistical clinical models)
  - associating
    - findings at the molecular biology level with
    - an specific valid diagnosis.

1.3.2. Brain Complexity: Alzheimer Disease

1.3.2. Brain Complexity: Alzheimer Disease

- 1907: Alzheimer, a psychiatrist, described
  the neuropathology of a presenile dementia.
- 1910: Kraepelin, a psychiatrist, baptized this
  as a new illness: Alzheimer disease.
- During the 20th century: the same neuropathology
  was found in senile dementia.
  Alzheimer disease became very important.
- 1990: molecular biology provided clues about mechanisms:
  - genetics of familial presenile forms
  - common late-onset Alzheimer disease:
    association of
    - apolipoprotein E-4 with
    - age of onset

1.3.2. Brain Complexity: Alzheimer Disease

- Currently Alzheimer disease is considered neurological.
  - Most articles about it are published in neurological journals by neurologists.
- Let's stretch reality and consider Alzheimer disease a psychiatric disease:
  - with known neuropathology and
  - clearly established boundaries, and
  - a good example of a psychiatric disease that follows the medical model, which Kraepelin proposed for psychiatric diseases.
- Research based on disease mechanisms in Alzheimer disease has been disappointing.

1.3.2. Brain Complexity: Alzheimer Disease

	Alzheimer	Schizophrenia
Neuropathology	Known for 100 years	Has failed
Borders	By neuropathology	Unknown
Validation	Neuropathology	How?
Treatment	Limited	Serendipity for 60 years, not specific
Research on molecular biology	Disappointing for last 25 years	No way of validating
Leading to personalizing	Currently impossible	Unclear when?

2. Drug Mechanisms For Personalizing Prescription

2. Drug Mechanisms for Personalizing Prescription

2.1. Drug Mechanisms
2.2. Current Pharmacogenetic Testing For Drug Mechanisms
2.3. Present vs. Future Pharmacogenetic Testing

2.1. Drug Mechanisms

(see the longer version of this section in the presentation "Introduction to Clinical Pharmacology")

2.1. Drug Mechanisms

2.1.1. Personal, Environmental and Genetic Factors
2.1.2. Pharmacodynamics and Pharmacokinetics
2.1.3. Efficacy and Safety
2.1.4. Interactions between 2.1.1, 2.1.2 and 2.1.3

2.1. Personal, Environmental and Genetic Factors

2.1.1. Personal, Environmental and Genetic Factors

- Classification according to three types of factors is somewhat arbitrary, but serves mnemonic purposes.
- This classification is not found in any pharmacology textbook.
- This terminology is used by Dr. de Leon in his articles.

First article using it: http://www.ncbi.nlm.nih.gov/pubmed/18687938
Article explaining it: http://www.ncbi.nlm.nih.gov/pubmed/18996200 with a pdf available http://uknowledge.uky.edu/psychiatry_facpub/43/

2.1.1. Personal, Genetic and Environmental Factors

- Personal (obtained from personal history):
  - Gender and age
  - Race (can reflect genetic variations)
  - Medical illnesses or pregnancy
- Environmental (potentially removable):
  - Smoking
  - Co-medication
  - Herbal supplements
  - Food and beverages
- Genetics: (assessed by genetic tests):
  - Genetic variations
  - Epigenetic variations (do not influence DNA sequence): They are poorly understood but may explain how environmental factors influence genetics.

2.1.2. Pharmacokinetics and Pharmacodynamics

2.1.2. Pharmacokinetics and Pharmacodynamics

- Pharmacokinetics:
  - Drug concentration (usually in blood)
  - Body to drug

- Pharmacodynamics:
  - Site of action
    (mainly brain receptors in psychiatry)
  - Drug to body

2.1.2. Pharmacokinetics and Pharmacodynamics

2.1.2.1. Pharmacokinetics
2.1.2.2. Pharmacodynamics

2.1.2.1. Pharmacokinetics

2.1.2.1. Pharmacokinetics

- Metabolic enzymes:
  - Functionalizing enzymes:
    Used to be called Phase I
    - oxidation,
    - reduction or
    - hydrolysis

    Most important: CYPs
  - Conjugation enzymes
    Used to be called Phase II
    Most important: UGTs

- Transporters:
  P-glycoprotein

2.1.2.2. Pharmacodynamics

2.1.2.2. Pharmacodynamics

- Psychiatric drugs produce reactions at:
  - The brain:
    - receptors
    - transporters
  - The periphery:
    - brain effects
    - receptors in the periphery
    - transporters in the periphery
    - other (lipid metabolism?)

2.1.3. Efficacy and Safety

2.1.3. Efficacy and Safety: Definition

- Efficacy is how well the desired effect is obtained in the patient.

http://www.ncbi.nlm.nih.gov/pubmed/15554250

- Safety's goal is to avoid adverse drug reactions (ADRs). Psychiatric textbooks use the old terminology "side effects" instead of ADRs.

2.1.4. Interactions

2.1.4. Interactions

- Dr. de Leon refers to interactions among:
  - Personal, Environmental and Genetic Factors
  - Pharmacokinetics and Pharmacodynamics
  - Efficacy and Safety
- These interactions are not discussed in textbooks.

2.4.1. Interaction of Personal, Environmental and Genetic Factors with Other Dimensions

- Personal factors can influence:
  - Pharmacokinetics and pharmacodynamics
  - Efficacy and safety
- Environmental factors can influence:
  - Pharmacokinetics and pharmacodynamics
  - Efficacy and safety
- Genetic factors can influence:
  - Pharmacokinetics and pharmacodynamics
  - Efficacy and safety

2.4.2. Interaction of Pharmacokinetics and Pharmacodynamics with Other Dimensions

- Pharmacokinetics can be influenced by:
  - Personal, environmental and genetic factors

  And influence both:
  - Efficacy and safety

- Pharmacodynamics can be influenced by:
  - Personal, environmental and genetic factors

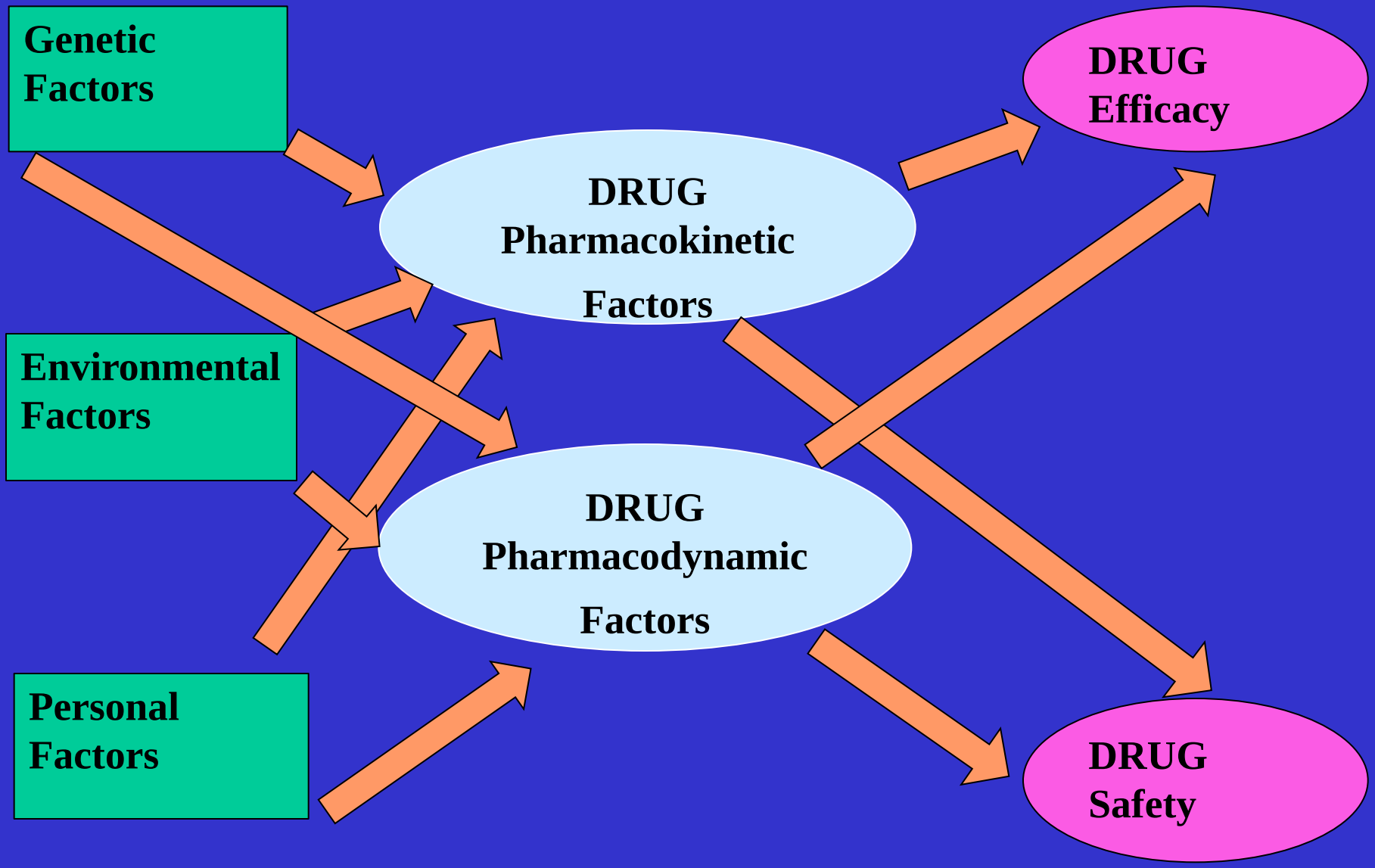
  And influence both:
  - Efficacy and safety

2.4.3. Interaction of Efficacy and Safety with Other Dimensions

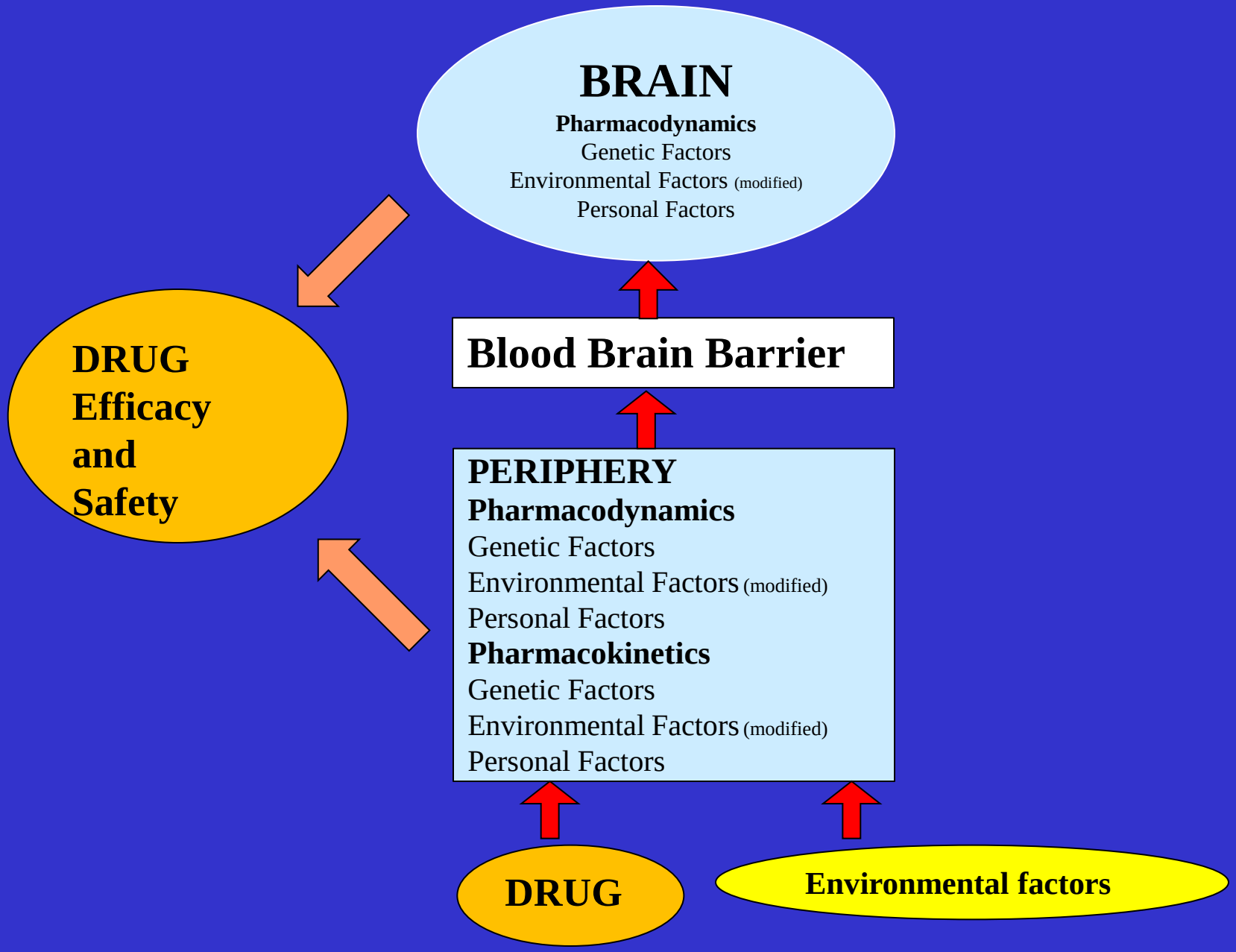
- Efficacy can be influenced by:
  - Personal, environmental and genetic factors
  - Pharmacokinetics and pharmacodynamics

- Safety can be influenced by:
  - Personal, environmental and genetic factors
  - Pharmacokinetics and pharmacodynamics

2.4. Interactions: Figure for Remembering Concepts



2.4. Interactions: Figure for Representing Concepts



2.4. Interaction of Efficacy and Safety with Pharmacokinetics and Pharmacodynamics

- Pharmacokinetics **facilitates** pharmacodynamics:
  - Sufficient drug concentration for efficacy.
  - Drug concentrations that are too high may contribute to poor safety in general.
- Pharmacodynamics determines:
  - Efficacy, when adequate drug concentration is present.
  - Safety, when concentration is sufficient for "toxicity". Specific ADRs in a patient are determined by pharmacodynamic factors.

2.2. Current Pharmacogenetic Testing for Drug Mechanisms

(see the longer version of this section in the presentation "Pharmacogenetic Testing in Psychiatry")

2.2. Current Pharmacogenetic Testing: Drug Mechanisms

- Pharmacological mechanisms:
  - Pharmacokinetic mechanisms:
    - The most important CYPs, and ready for clinical practice for some drugs: CYP2D6 & CYP2C19
    - Other: P-glycoprotein is not ready for clinical practice. http://www.ncbi.nlm.nih.gov/pubmed/26111722
  - Pharmacodynamic mechanisms:
    - HLA: Carbamazepine & HLA-B*15:02 in East Asians
    - Other: Receptors/transporters are involved in neurotransmission, but not ready for clinical practice (see next slide).

2.2. Current Pharmacogenetic Testing: Drug Mechanisms

- Pharmacogenetic tests for receptors/ transporters involved in neurotransmission:
  - are marketed in the USA and Europe
  - no guidelines recommend them
  - scientific information is limited:
    - no understanding of genotype/phenotype relationships
    - no understanding of how environmental and personal factors influence phenotype
    - frequently based on non-replicated studies

2.3. Current vs. Future Pharmacogenetic Testing

2.3. Current vs. Future Pharmacogenetic Testing

2.3.1. Current vs. Future Pharmacogenetic Testing
2.3.2. Current Prescription vs. Future Integrated Personalized Prescription

2.3.1. Current vs. Future Pharmacogenetic Testing

This section is taken from a 2014 article

http://www.ncbi.nlm.nih.gov/pubmed/24196844

Pre-published Version: http://uknowledge.uky.edu/psychiatry_facpub/19/

2.3.1. Current vs. Future Pharmacogenetic Testing

2.3.1.1. Current Pharmacogenetic Testing

2.3.1.2. Future Pharmacogenetic Testing

2.3.1.1. Current Pharmacogenetic Testing

2.3.1.1. Current Pharmacogenetic Testing

- The ideal is large RCTs seeking to establish
  - classic proof of concept in the clinical environment, and/or
  - cost-benefit studies,

  which will not be conducted due to:
    - high costs, and
    - lack of funding mechanisms.
- Progressively ↓ genotyping costs.
- Solution: genotyping studies using comparisons with historical data.

2.3.1.1. Current Pharmacogenetic Testing

- Two ways to implement pharmacogenetic testing:
  - drug selection
  - drug dosing:
    - physician select the drug
    - the test personalizes the dose

- Personalizing drug selection is much more complex than personalizing drug dosing.

2.3.1.1. Current Pharmacogenetic Testing

2.3.1.1.1. Personalizing Drug Selection

2.3.1.1.2. Personalizing Drug Dosing

2.3.1.1.1. Personalizing Drug Selection

2.3.1.1.1. Personalizing Drug Selection

- Personalizing drug selection:
  - Selecting the “ideal drug” is very distant in psychiatry.
  - Eliminating some drugs from consideration for some patients is currently happening:
    - pharmacogenetic gene:
      CYP2D6 UM: do not administer a TCA
    - pharmacodynamic gene:
      HLA-B*15:02: do not administer carbamazepine

2.3.1.1.2. Personalizing Drug Dosing

2.3.1.1.2. Personalizing Drug Dosing

- Personalizing drug dosing is:
  - easier when
    - the drug follows linear kinetics and
    - has a narrow therapeutic window.
  - not practical for:
    - wide-therapeutic-window drugs, because physicians may be arbitrary in dosing.

.

2.3.1.2. Future Pharmacogenetic Testing

2.3.1.2. Future Pharmacogenetic Testing

- Pharmacogenomics, even if it includes epigenetic factors, should be considered a piece of a complex puzzle including:
  - environmental/personal factors
  - pharmacokinetics/pharmacodynamics
  - efficacy/safety (dose-related versus idiosyncratic ADRs), and
  - therapeutic window.

= Integrated Personalized Prescription

2.3.2. Current Prescription vs. Future Integrated Personalized Prescription

2.3.2. Current Prescription versus Future Integrated Personalized Prescription

2.3.2.1. Current Prescription

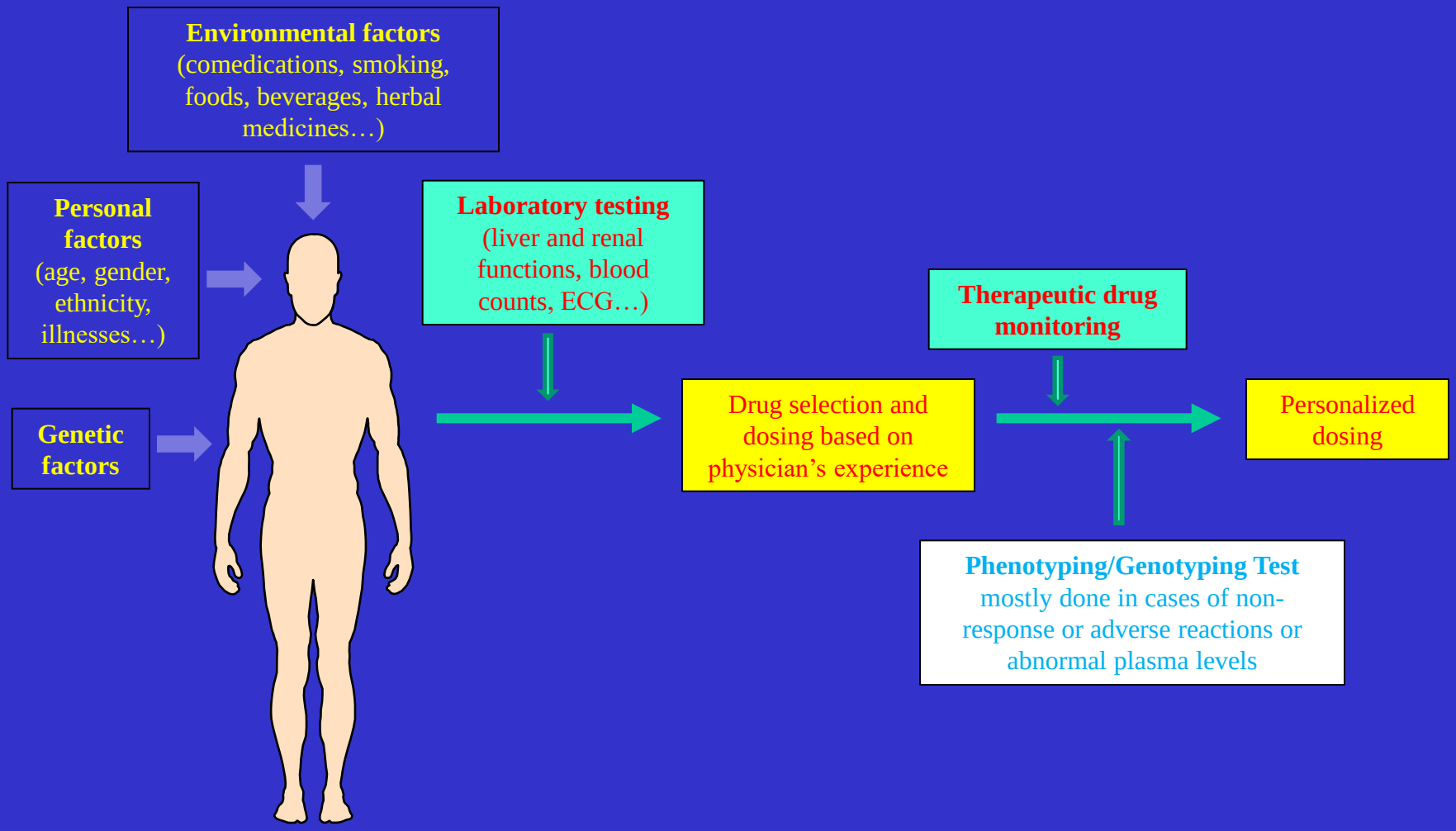
2.3.2.2. Future Integrated Personalized Prescription

2.3.2.1. Current Prescription

2.3.2.1. Current Prescription

- Current drug selection and dosing:
  - Drug selection is based on the physician's experience.
  - Dosing is based on the physician's experience, or it can be personalized using TDM and/or genotyping tests.
- Current genotyping:
  - non-response,
  - ADR, or
  - abnormal TDM.

2.3.2.1. Current Prescription



2.3.2.2. Future Integrated Personalized Prescription

2.3.2.2. Future Integrated Personalized Prescription

- Comprehensive genotyping will assist:
  - Personalized drug selection and personalized dosing
  - TDM (a phenotyping test) will lead to additional improvement in personalized dosing.

2.3.2.2. Future Integrated Personalized Prescription

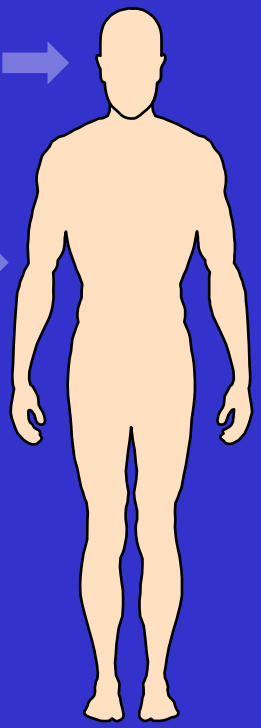
- Comprehensive genotyping:
  - drug response: pharmacokinetic genes
    pharmacodynamic genes
  - disease genes (biomarkers)
    (unlikely in the short term for psychiatry)
- Genotyping techniques will be:
  - quality-controlled
  - able to provide quick results
  - available to current and future physicians.

2.3.2.2. Future Integrated Personalized Prescription

Environmental factors (comedications, smoking, foods, beverages, herbal medicines…)

Personal factors (age, gender, ethnicity, illnesses…)

Genetic factors



Laboratory testing (liver and renal functions, blood counts, ECG…)

Personalized drug selection and **personalized** dosing

Therapeutic drug monitoring

Additional improvement in personalized dosing

Comprehensive genotyping
- Genes predisposing to diseases
- Genes involved in pharmacokinetics, pharmacodynamics, safety and efficacy of drugs
- Quality controlled (if possible two different genotyping methods)
- Quick; results available for current and future treating physicians

Phenotyping test
mostly done in cases of abnormal plasma levels not explained by genotyping

3. Clinical Subgrouping for Personalized Prescription

3. Clinical Subgrouping for Personalized Prescription

3.1. Basis: Descriptive Psychopathology
3.2. An Example using Schizophrenia
3.3. Strengths and Weaknesses

3.1. Clinical Subgrouping: Based on Descriptive Psychopathology

3.1. Clinical Subgrouping for Personalized Prescription: Basis

- Past attempts to personalize psychiatric treatments based on the clinical profile of the patient remain ignored.
- They are based on what is called "descriptive psychopathology"
  - definition (Berrios) http://www.ncbi.nlm.nih.gov/pubmed/6739628
  - "forgotten language of psychiatry" (Ban)

http://inhn.org/e-books/thomas-a-ban-neuropsychopharmacology-and-the-forgotten-language-of-psychiatry.html

  - the language for psychiatric science:

http://www.ncbi.nlm.nih.gov/pubmed/25849592

3.1. Clinical Subgrouping for Personalized Prescription: Basis

- The idea behind these ignored approaches is that diseases, such as:
  - schizophrenia and
  - depression,

  are not diseases but syndromes
  - that can be carved out by sophisticated use of clinical symptoms into more specific diseases, better related to treatment response.

3.1. Clinical Subgrouping for Personalized Prescription: Basis

- Ban: a traditional psychopharmacologist who defended the concept that a disease's clinical profile can be used to group patients according to response.
  He has focused on: □ depression and
  □ schizophrenia (next slides)
  PubMed articles: http://www.ncbi.nlm.nih.gov/pubmed/2892227
  http://www.ncbi.nlm.nih.gov/pubmed/17970531
  Ban's archives: http://inhn.org/archives/ban-collection.html
  Ban's e-books: http://inhn.org/e-books.html

3.2. Clinical Subgrouping: An Example using Schizophrenia

3.2. Clinical Subgrouping for Schizophrenia

- Ban's schizophrenia approach: based on Leonhard, who is ignored by most US textbooks.
- Sometimes these are called the "Berlin School";
  - Wernicke: Kraepelin's competitor
  - Kleist:
    - Wernicke's disciple
    - Leonhard's mentor
  - Leonhard: 3 types of psychoses
    - schizophrenia
    - cycloid psychoses
    - phasic psychoses: melancholia
      manic-depressive

2016 familial study supports validity.

http://www.ncbi.nlm.nih.gov/pubmed/26707865

3.2. Clinical Subgrouping for Schizophrenia

- For Leonhard, schizophrenia is a syndrome.
  - Systematic schizophrenias are non-genetic:
    including
    - paraphrenias
    - hebephrenias
    - catatonias
  - Unsystematic schizophrenias are genetic:
    including
    - cataphasia
    - affect-laden paraphrenia
    - periodic catatonia

3.2. Clinical Subgrouping for Schizophrenia

- Leonhard's schizophrenia & response:
  - 474 Norwegian patients: http://www.ncbi.nlm.nih.gov/pubmed/14163581
    - <1/4 of systematic schizophrenia
    - >4/5 of unsystematic schizophrenia

  responded to antipsychotics (first generation)
- International survey of 768 patients:

  Tardive dyskinesia: http://www.ncbi.nlm.nih.gov/pubmed/2866562
    - 13.3% of systematic schizophrenia
    - 4.3% of unsystematic schizophrenia
- 50 German patients: http://www.ncbi.nlm.nih.gov/pubmed/1361971
    - antipsychotics did not change the prognosis
    - when compared with Leonhard's observations.

3.3. Clinical Subgrouping: Strengths and Weaknesses

3.3. Clinical Subgrouping: Strengths and Weaknesses

- Conclusion of these long-term outcome studies: systematic schizophrenias do not respond well, at least to first-generation antipsychotics.
- Weaknesses: did not use □ blinding or
  □ placebo
- Strengths:
  - □ sophisticated clinicians
  - □ no reason to think that these clinical researchers were biased toward finding greater response to antipsychotics in unsystematic schizophrenia, as Leonhard developed his classification in the pre-neuroleptic era.

3.3. Clinical Subgrouping: Strengths and Weaknesses

- Due to these methodological weaknesses:
  - these studies
  - and other long-term outcome studies

  using sophisticated clinical subgrouping remain forgotten
  by current psychopharmacologists
  who only value RCTs,
  which are usually shot-term studies.

3.3. Clinical Subgrouping: Strengths and Weaknesses

- RCTs have made limited contributions in psychiatry.
  - Psychopharmacological drugs were discovered by sophisticated clinicians without using well-controlled designs.
  - RCTs brought to psychiatry:
    - no revolutionary drugs
    - some second-generations drugs with possibly some better ADR profiles but of doubtful greater efficacy
    - accusations of corruption by pharmaceutical companies.

3. Clinical Subgrouping for Personalized Prescription

- Dr. de Leon thinks that
  - it would be interesting to incorporate some of these attempts to subdivide:
    - schizophrenia and
    - major depression

    in future well-controlled pragmatic trials of psychotropic drugs.
  - it is not easy, requiring intensive clinical training of psychiatrists involved in the diagnosis and assessment of patients.

4. Conclusions

4. Conclusions

- Personalized medicine has finally (2010-5) been discussed in psychiatric journals, but focused on the promise of using disease mechanisms to personalize treatment.
- Psychiatric disorders such as:
  - schizophrenia and
  - depression

  are not diseases, in the medical sense, and are probably more like syndromes.

4. Conclusions

- If one focuses on Alzheimer disease, which is closer to the concept of brain disease,
  - mechanistic approaches are disappointing, and
  - personalized prescription: not in 10-20 years.
- Instead of spending much time and effort focusing on the mechanisms of diseases, psychiatrists should:
  - learn more about personalizing prescription using the drug mechanisms that are common among syndromes, and
  - reassess sophisticated clinical subgrouping.

4. Conclusions

- Pharmacogenetic tests may bring definitive but modest improvements using:
  - pharmacokinetic mechanisms to personalize drug treatment with a few psychiatric drugs, or
  - pharmacodynamic mechanisms for personalizing drug selection (ruling out) for even fewer psychiatric drugs.

4. Conclusions

- Even if one focuses only on using drug mechanisms to personalize prescription in psychiatry, Dr. de Leon thinks it is a very complex process, based on:
  - the individuality of each patient, differences in:
    - genetics
    - environmental
    - personal factors
  - the individuality of each drug, differences in:
    - pharmacokinetic mechanisms
    - pharmacodynamic mechanisms

  explained by the arbitrariness of evolution.

4. Conclusions

Recipe for using drug mechanisms to personalize prescription:

1) a drug's pharmacokinetic & pharmacodynamic mechanisms are behind its efficacy and safety;
2) genetic, environmental and personal variables influence drug pharmacokinetic & pharmacodynamic mechanisms and through them its efficacy and safety;
3) personalizing drug selection is much more complex than personalizing drug dosing;
4) in the process of personalizing drug selection, eliminating a drug is easier than choosing a drug;
5) personalizing dosing is easier when the drug follows linear kinetics and has a narrow therapeutic window; and
6) personalizing dosing in wide-therapeutic-window drugs is not practical; physicians may be very arbitrary in dosing.

References

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3) 2014 article http://www.ncbi.nlm.nih.gov/pubmed/24196844 describes current and future pharmacogenomics in psychiatry.

4) 2012 article http://www.ncbi.nlm.nih.gov/pubmed/22367661 compares personalized medicine with EBM.

5) 2009 article http://www.ncbi.nlm.nih.gov/pubmed/18996200 describes personalized prescription in psychiatry according to pharmacological mechanisms.

Free versions at Research Gate https://www.researchgate.net/home or http://uknowledge.uky.edu/do/search/?q=author_lname%3A%22de%20Leon%22%20AND%20author_fname%3A%22Jose%22&start=0&context=1674591&sort=date_desc

Questions

-Please review the 10 questions in the pdf titled "Questions on the Presentation Personalized Medicine in Psychiatry".

-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 Power Point presentation once again to reinforce the pharmacological concepts.

Thank you

for surviving the complexity of Dr. de Leon's ideas
in personalized medicine.

Answers

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