TOWARDS A CLINICAL METHODOLOGY FOR NEUROPSYCHOPHARMACOLOGICAL RESEARCH
Development of Neuropsychopharmacology
1950s

PHARMACOTHERAPY (1952 - 1957)

PSYCHOPHARMACOLOGY

NEUROTRANSMITTERS (1952-1960)

SPECTROPHOTOFUORIMETER (1955)

NEUROPHARMACOLOGY

NEUROPSYCHOPHARMACOLOGY (1957)
Birth of composite discipline
NEUROPSYCHOPHARMACOLOGY LINKS THE EFFECT OF A DRUG ON MENTAL ILLNESS WITH ITS EFFECT ON BRAIN STRUCTURES INVOLVED IN ITS MODE OF ACTION

KNOWLEDGE

PATHOPHYSIOLOGY OF ILLNESS ➔ MORE SELECTIVE DRUG
NEUROTRANSMITTER ERA
First Epoch In the History of Neuropsychopharmacology
NEUROTRANSMITTER ERA
NEUROPHARMACOLOGY

Spectrophotofluorimeter & Receptor Binding Assays

Neurotransmitter dynamics
metabolism
regional distribution
effect of drugs on uptake & release
Affinity of drugs to neurotransmitter receptors
NEUROTRANSMITTER ERA
PSYCHOPHARMACOLOGY

Rating Scales & Consensus Based Diagnoses

Statistical Methodology (RCT)
efficacy
efficacy in more than one diagnosis
BY LINKING THE MODE OF ACTION OF A DRUG WITH A PHARMACOLOGICALLY HETEROGENEOUS POPULATION, NEUROPSYCHOPHARMACOLOGICAL RESEARCH PROVIDED RELEVANT FEEDBACK ONLY TO THE DEVELOPMENT OF DRUGS WITH DIFFERENT ADVERSE EFFECTS
FROM THE NEUROTRANSMITTER TO THE GENETIC ERA

GAP BETWEEN NEUROPHARMACOLOGY WITH CAPABILITY TO TAILOR DRUGS TO RECEPTOR AFFINITIES BY GENETIC TECHNOLOGY AND PSYCHOPHARMACOLOGY WITH METHODOLOGY RESTRICTED TO DEMONSTRATION OF THERAPEUTIC EFFICACY

INCONSISTENT AND CONFLICTING FINDINGS IN MOLECULAR GENETIC RESEARCH
FROM THE NEUROTRANSMITTER TO THE GENETIC ERA

RECOGNITION THAT:

PRIMARY TARGETS OF PSYCHOTROPIC DRUGS ARE ENCODED BY GENES THAT HAD BEEN IDENTIFIED

ANY CLINICAL ENTITY THAT CORRESPONDS WITH A TREATMENT RESPONSIVE POPULATION IS SUITABLE FOR THE GENERATION OF GENETIC HYPOTHESES OF MENTAL ILLNESS

PROGRESS IN MOLECULAR GENETIC RESEARCH DEPENDS ON IDENTIFYING PHARMACOLOGICALLY HOMOGENEOUS POPULATIONS
ALTERNATIVE APPROACHES

BREAK-UP INTO SIMPLE BIOLOGICAL COMPONENTS

RE-CONCEPTUALIZE IN DISCRETE BIOLOGICAL DEFICITS

*Alternative Phenotypes for Schizophrenia*

Abnormality of smooth pursuit eye movement; short arm of chromosome 5
P-50 evoked response deficit; $\alpha_1$-nicotinic acid receptor
on long arm of chromosome 15

GENETIC PSYCHIATRIC NOSOLOGY
TOWARDS THE COMPOSITE DIAGNOSTIC EVALUATION (CODE) SYSTEM

RECOGNITION THAT:

THERE IS NO ALTERNATIVE METHODOLOGY TO PSYCHIATRIC NOSOLOGY FOR CLASSIFYING MENTAL PATHOLOGY IN A CLINICALLY RELEVANT MANNER

IDENTIFICATION OF TREATMENT RESPONSIVE FORMS OF ILLNESS IS PREREQUISITE FOR PROGRESS

DIFFERENTIAL RESPONSIVENESS TO A PSYCHOTROPIC DRUG WITHIN A DIAGNOSTIC CATEGORY CANNOT BE EXPLAINED BY PHARMACOKINETIC DIFFERENCES
TOWARDS THE CODE SYSTEM

INCONSISTENT FINDINGS WITH LINEAR REGRESSION EQUATIONS IN WHICH RATING SCALE SCORES WERE USED

FRANK FISH’S (1964) FINDINGS THAT 86% OF PATIENTS WITH AFFECT-LADEN PARAPHRRENIA & LESS THAN 25% OF PATIENTS WITH SYSTEMATIC SCHIZOPHRENIA RESPONDED TO NEUROLEPTIC PHENOTHIAZINES

DEMOnSTRATION THAT CONSENSUS-BASED DIAGNOSES (DSM-IV) COVER-UP THEIR COMPONENT DIAGNOSES

Vital Depression
Affect-laden Schizophrenia
THE CODE SYSTEM

METHODOLOGY FOR THE IDENTIFICATION OF TREATMENT RESPONSIVE FORM OF ILLNESS BY UNCOVERING DIAGNOSES

VOCABULARY

PSYCHOPATHOLOGIC SYMPTOM PROFILE

STRUCTURED INTERVIEW

DIAGNOSTIC PROFILES

DIAGNOSTIC ALGORITHMS

RATING SCALE FOR SEVERITY

SEVERITY SCORE

READILY ACCESSIBLE INFORMATION RELEVANT TO THE DIAGNOSTIC PROCESS FROM THE LOWEST TO THE HIGHEST LEVEL OF DECISION MAKING

CODE-AD, DD, HD, SD
PETER GASZNER
THOMAS A. BAN

CODE-HD
Composite Diagnostic Evaluation of Hyperthymic Disorders

BUDAPEST
1998
CODE-DD
1896-1987

VOCABULARY
90 items (codes)

STRUCTURED INTERVIEW

DIAGNOSTIC ALGORITHMS
25 classifications

RATING SCALE FOR SEVERITY
40 items (codes)

VALIDITY

1st Study  239 pts  99.6%
2nd Study  322 pts  97.2%

RELIABILITY

1st Study  87.2%
2nd Study  100.0%

Translations & adaptations from the English original: Estonian, French, Hungarian, Italian, Polish and Portuguese
Thomass A. BAN

CODE-DD

Evaluation diagnostique composite des troubles dépressifs

Edition française
Françoise Ferrero
avec la collaboration de
Marc-Antoine Crocq et Jean-François Dreyfus

Editions Médecine et Hygiène
Genève
1987
HYPOTHESES

MAJOR DEPRESSION IS A BROAD DIAGNOSTIC CATEGORY
If depression would be characterized by unmotivated depressed mood, depressive evaluations, and lack of reactive mood changes, from the 322 patients with the DSM-III-R clinical diagnosis of major depression only 119, i.e., 37% would have qualified for depression.

MAJOR DEPRESSION IS MORE THAN ONE FORM OF ILLNESS
From the 322 patients only 95 (29.5%) fulfilled definite criteria of Kraepelin’s depressive states and 45 (14%) Schneider’s vital depression with little overlap between the two forms of illness.
CODE-UD
Hippocrates (460-377BC) TO DSM-IVTM (1994)
Maximizes potential of uncovering diagnoses
MELANCHOLIA

<table>
<thead>
<tr>
<th>Period</th>
<th>Year</th>
<th>Description</th>
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<tbody>
<tr>
<td>Hippocrates</td>
<td>5th BC</td>
<td>Chronic Mental Disease</td>
</tr>
<tr>
<td>Sauvages</td>
<td>1769</td>
<td>Insanity With Disturbed Cognition</td>
</tr>
<tr>
<td>Cullen</td>
<td>1769</td>
<td>Insanity With Disorder of Judgment</td>
</tr>
<tr>
<td>Heinroth</td>
<td>1818</td>
<td>Insanity With Depression of Emotions</td>
</tr>
<tr>
<td>Esquirol</td>
<td>1838</td>
<td>Lypemania (Melancholia) vs.Monomania</td>
</tr>
</tbody>
</table>
CODE SYSTEM
Methodology for the identification of treatment responsive form of illness if covered up by consensus-based diagnoses

NOSOLOGIC MATRIX
Methodology for the development of empirically derived pharmacologically valid classification
Fritz Freyhan
First proposed pharmacological re-evaluation of Kraepelinian nosology with the employment of target symptoms
NOSOLOGIC HOMOTYPING
by
NOSOLOGIC MATRIX
on the basis of
PSYCHOPATHOLOGIC SYMPTOMS &
PSYCHIATRIC NOSOLOGY
IT WAS IN 2002 FIRST THAT NOSOLOGIC HOMOTYPING A METHODOLOGY FOR PHARMACOLOGICAL RE-EVALUATION OF PSYCHIATRIC NOSOLOGY WAS PROPOSED

NOSOLOGIC HOMOTYPES ARE IDENTICAL IN ELEMENTARY UNITS (PSYCHOPATHOLOGICAL SYMPTOMS) AND ARE assigned the same position in the nosologic matrix constructed with the employment of three nosologic organizing principles: TOTALITY TEMPORAL ORGANIZATION SPATIAL ORGANIZATION
NOSOLOGIC MATRIX
Elementary Units

The elementary units of mental illness in the nosologic matrix are psychopathologic symptoms (1920s)

Psychopathologic symptoms are accessible to pharmacologic manipulation to psychotropic drugs (1950s)

Psychotropic drugs are substances with an effect on the transmission of impulses at the synaptic cleft (1950s)

Psychopathologic symptoms are manifestations in the processing of mental events with each symptom representing a distinct pathology (2002)

Each psychopathologic symptom profile is a potential phenotype of a mental disorder
The psychopathologic symptom profile is derived by the determination of the “presence” or “absence” of psychopathologic symptoms included in a comprehensive list of psychopathologic symptoms.
PSYCHOPATHOLOGIC SYMPTOM SCALES

Afferent (perceptual-cognitive) Scale 1
Central (relational-affective) Scale 2
Efferent (adaptive-psychomotor) Scale 3

Some of the symptoms of Scale 1

accelerated thinking
agrammatism
akoasma(s)
alogia
anesthesia
asynedetic thinking
auditory hallucination(s)
autistic delusion(s)
autoscopic hallucination(s)
bizarre delusion(s)
circumstantial thinking
coenesthetistic hallucination(s)
command hallucination(s)
Nosologic Matrix
FIRST ORGANIZING PRINCIPLE

TOTALITY (Esquirol 1838)
Mania vs Monomania

Esquirol 1838 Total vs. Partial
Partial insanity: Personality remains preserved

Westphal 1878 True vs. Abortive
Abortive insanity: Insight that thinking/feelings/actions are pathological

Wernicke 1899 Universal vs. Selective
Selective insanity: Disorientation is restricted to allo- or auto- or somatopsychic

Leonhard 1957 Complete vs. Incomplete
Incomplete: Restricted to one or two components of the psychic reflex
TEMPORAL ORGANIZATION (Kraepelin 1899)
Dementia Praecox vs. Manic-depressive Inanity

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tbody>
<tr>
<td>Attacks</td>
<td>episodes last from minutes to hours</td>
</tr>
<tr>
<td>Phases</td>
<td>episodes last from days to years</td>
</tr>
<tr>
<td>Periods</td>
<td>phases recur with regularity</td>
</tr>
<tr>
<td>Thrusts</td>
<td>acute events yield lasting changes</td>
</tr>
<tr>
<td>Continuous process</td>
<td>chronic events yield differentiated end-states</td>
</tr>
<tr>
<td>Progressive deterioration</td>
<td>chronic events yield de-differentiation</td>
</tr>
</tbody>
</table>
Nosologic Matrix

THIRD ORGANIZING PRINCIPLE

SPATIAL ORGANIZATION-POLARITY (Leonhard 1957)
Manic-depressive disease vs. Pure mania/melancholia

Bipolar (polymorph/multiform)
swings between two poles of mood/emotions/motility;
displays continuously changing variable picture

Unipolar (monomorph/pure)
restricted to one pole of mood/emotions/motility;
displays same picture within & across episodes
NOSOLOGIC HOMOTYPES

NOSOLOGIC HOMOTYPES BASED ON THE NOSOLOGIC MATRIX ARE MORE HOMOGENEOUS POPULATIONS THAN ANY OF THE DIAGNOSTIC POPULATIONS IDENTIFIED BY THE AVAILABLE DIAGNOSTIC INSTRUMENTS

THE INFORMATION GENERATED BY THE USE OF THE NOSOLOGIC MATRIX WOULD ALLOW THE COMPLETION OF THE RE-EVALUATION OF KRAEPELINIAN DIAGNOSTIC CONCEPTS STARTED BY PSYCHIATRISTS AT THE HEIDELBERG CLINIC IN THE 1920s
NOSOLOGIC HOMOTYPES

IF THE INFORMATION COLLECTED BY THE NOSOLOGIC MATRIX WOULD NOT IDENTIFY PHARMACOLOGICALLY OR GENETICALLY HOMOGENOUS POPULATIONS IT WOULD INDICATE THAT PSYCHOPATHOLOGY AND PSYCHIATRIC NOSOLOGY HAVE NOTHING TO OFFER TO BIOLOGICAL PSYCHIATRIC RESEARCH AND GENERAL PSYCHOPATHOLOGY SHOULD BE REPLACED BY A FUNCTIONAL PSYCHOPATHOLOGY AND THE NOSOLOGICAL DISEASE MODEL BY A REACTION-FORM BASED DISEASE MODEL AS SUGGESTED BY VAN PRAAG (1992, 2000)
NOSOLOGIC HOMOTYPES

If the information collected by the nosologic matrix identifies pharmacologically or genetically homogenous populations it would indicate that nosological homotypying could provide the key for the delineation of biologically meaningful disease categories and by linking the mode of action of psychotropic drugs to pharmacologically homogenous populations it would break the impasse in the progress of neuropsychopharmacological research, pharmacotherapy, and molecular genetic research in mental illness.
NOSOLOGIC HOMOTYPES

CONSIDERING THAT NOSOLOGICAL HOMOTYPES ARE DEFINED IN TERMS OF THEIR EFFECT ON PROCESSING OF MENTAL EVENTS, AND PSYCHOTROPIC DRUGS ARE DEFINED IN TERMS OF THEIR EFFECTS ON SIGNAL TRANSADUCTION IN THE BRAIN, THE EMPIRICALLY DERIVED DIAGNOSTIC CATEGORIES COULD PROVIDE CLINICAL ENTITIES WHICH ARE SUITABLE FOR TESTING HYPOTHESES RELEVANT TO THE RELATIONSHIP BETWEEN PROCESSING OF MENTAL EVENTS AND SIGNAL TRANSDUCTION IN THE CENTRAL NERVOUS SYSTEM
NOSOLOGIC HOMOTYPES

NOSOLOGIC HOMOTYPING COULD OPEN A NEW PERSPECTIVE FOR THE DEVELOPMENT OF A PSYCHIATRY IN WHICH MENTAL PATHOLOGY IS PERCEIVED IN TERMS OF PATHOLOGY IN SIGNAL TRANSDUCTION IN THE BRAIN AND FOR THE DEVELOPMENT OF A RATIONAL PHARMACOTHERAPY OF MENTAL ILLNESS