MENTAL HEALTH (PSYCHIATRY) AND PHARMACEUTICALS

(In a Historical Perspective)

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Developments that led to the birth of drug industry

John Dalton (1766 – 1844): Elementary units of all matter in the universe are indivisible and indestructible atoms (1808).

Friedrich August Kekulé (1829 –1896):chemical structure allowed for the determination of the bonding order of all of the atoms in a molecule (1857 – 1858).

Instrumental to the birth of drug industry

William Henry Perkins (1838 – 1907): accidental discovery of aniline purple (1856), the first artificial dye in history.

Emergence of dye industry: Bayer and Ciba (1859), Geigy and Sandoz (1862).

Extension of activities of some dye companies to pharmaceuticals: Ciba (1890), Bayer (1896).

Legal underpinning: British Corporate Law (1844, 1855) control passed from Government to Court; protection of investors' personal assets from the consequences of their corporate behavior.

Drugs in psychiatry: First of three sets

2nd part of 19th century

Morphine (apomorphine) + hyoscine (scopolamine) subcutaneously (Wood 1855):control of excitement, agitation and aggression.

Potassium bromide (Lockock 1857): relieving restlessness, anxiety and tension.

Chloral hydrate (Liebreich 1869): calming and inducing sleep.

Paraldehyde (Cervello 1882): calming and inducing sleep.

First set: Effects on psychiatry:

Day and night-time sedation: replacement of physical restraint by pharmacological means.

Control of behavior: collection of information and the study of patients throughout their illness.

Information collected: psychopathology and psychiatricnosology provide a foundation for psychiatry.

Psychopathology:deals with symptoms and signs (elementary units) of mental illness.

Psychiatric nosology: deals with rules of separating subpopulations (with predictive validity) and classifying these subpopulations.

Second set: Effectson psychiatry

(1926 – 1938)

Thiamine – Vitamin B1 (Jansen and Donath 1926): Marked decrease of patients in mental hospitals with amnestic syndrome due to Wernicke's (1881) disease (cerebral beriberi).

Penicillin (Fleming 1929): Virtual disappearance of patients in mental hospitals with cerebral syphilis (Stokes 1944).

Nicotinic acid – Vitamin B3 (Elvehjem et al. 1937): Virtual disappearance of patients in mental hospitals with cerebral pellagra.

Diphenylhydantoin (Putnam and Merritt 1937-38): Marked decrease of patients in mental hospitals with epilepsy.

Overall: By the 1950s changes in the diagnostic distribution of patient in psychiatric hospitals: proportion of functional psychoses increased.

Third setof drugs

1950s

Lithium (Cade 1949): Mania

Chlorpromazine (Delay and Deniker 1952): Schizophrenia

Reserpine (Bleuler and Stoll 1953; Kline 1954): Schizophrenia

Meprobamate (Berger 1955): Anxiety

Imipramine (Kuhn 1957): Depression

Iproniazide (Loomer, Saunders and Kline 1957): Depression

Chlordiazepoxide (Sternbach 1960): Anxiety

Neuropharmacology

1950s

Studies of the molecular substrate involved in the mode of action of psychotropic drugs (Ban 2011).

Shift in understanding of signal transmission in CNS from purely electrical to chemically mediated event.

Seven chemical neurotransmitters identified in CNS: ACh, DA, GABA, NE, 5HT,GABA and Substance P.

Recognition of chemical mediation at the site of the synapse.

Introduction of spectrophotofluorometer (Bowman et al. 1955) with resolution power to measure drug-induced changes in concentration of cerebral monoamines, such as NE and 5-HT in brain.

Neuropsychopharmacology

1950s

Studies the mode of action of psychotropic drugs for obtaining information on the biochemical underpinning of mental pathology in order to develop rational pharmacological treatments (Hollister 1996; Wikler 1957).

Demonstration: iproniazid, a MAOI,increased whereas reserpine decreased cerebral monoamines, such as NE and 5-HT (Pletscher et al. 1955, 1956; Besendorf and Pletscher 1956).

Treatment: iproniazid induced euphoria in some tubercular patients (Flaherty 1952; Selikoff et al. 1952) whereas reserpine induced depressed mood in some hypertensives (Bunney and Davis 1965; Kline 1968).

Mood is mediated by 5-HT and NE.

Pharmacologicalheterogeneity

Introductionof the third set of drugs focused attention on the pharmacological heterogeneity of psychiatric (Kraepelinian) diagnoses.

Heterogeneity was so great that it took eight years (1952-1960) to demonstrate the therapeutic efficacy chlorpromazine in schizophrenia (Casey et al. 1960) and imipramine (1957– 1965) in depression (Klerman and Cole 1965).

Pharmacological re-evaluation
Fritz Freyhan 1959

Recognized pharmacological heterogeneity within diagnoses.

Recommendedpharmacological re-evaluation of diagnoses.

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Marketing vs Education

Objective of marketing: to get a product prescribed in the widest possible population.

Objective of education: to guide the judicious and discriminate use of available drugs.

Identification of treatment responsive (sub)population

Successful education &neuropsychopharmacological research are dependent on therapeutic effects of a pharmacologically homogeneous population, i.e., identification of the treatment responsive population to a drug.

Demonstration of therapeutic efficacy in largest possible population

In keeping with marketing interests astatistical methodology the randomized clinical trial was adopted (first by the British school of psychiatry) for the demonstration of therapeutic efficacy in a diagnostically defined but pharmacologically heterogeneous population.

Legislation

Safety and Efficacy

1906 **Pure Food and Drug Act - Safety requirements.**

1907 – 1961 **Separation of prescription from over-the-counter medications**

1962 **Kefauver – Harris Amendment - Safety and Efficacymust be demonstrated.**

US FDA: drug must show statistically significant difference to placebo in two pivotal double-blind, randomized clinical trials which are of adequate sample size and statistical power.

Kefauver-Harris Amendment

(1) drugs have to be produced in accordance with sound manufacturing practices;

(2) the distribution and the use of investigational drugs have to be adequately controlled;

(3) prescription drug labelling and advertising have to confirm to governmental approval; and

(4) provision has to be made by the manufacturer (distributor) for keeping records and reporting that an ineffective or unsafe drug could be removed.

Other Legislation

1964 **Helsinki Declaration – Code of ethics for experimentation in humans.**

1965 **Institutional Review Board (IRB) - resolution of the National Advisory Health Council.**

1966 **Informed Consent - Goddard Amendment.**

Effects of FDA requirements

Diagnostic end points which can be reliably identified.

Rating sales which can detect and document changes.

Consensus-based diagnoses replaced prototype-based and nosology derived diagnoses.

Rating scales replaced psychopathology.

Pharmacotherapy became dominant treatment.

Thinkingin psychiatry shifted from psychological to biological.

Pharmaceutical research industry

1980s

Replacement of first generation drugs with second generation drugs: typical antipsychotics with atypical antipsychotics andtricyclic antidepressants withSSRIs.

A pharmaceutical research industry was created in whichsingle-center isolated clinical studies were replaced by multi-center centrally coordinated clinical investigations in which individual contributions were restricted to a small and insignificant proportion of the total sample; the collected data were owned by drug companies and communication of findings was controlled by industrial product managers.

Confounding of marketing and education

Since findings in studies generated in this pharmaceutical research industry provide the evidence-basedinformation for both, marketing and education by the dawn of the 21st century education in the pharmacotherapy of mental illness has become confounded with the marketing of psychotropic drugs.

The control of information in the pharmacological research industry is so tight that clinical researchers are legally bound -- by signed non-disclosure agreements -- not to disclose information without the permission of the sponsor; and educators in pharmacotherapy are restricted to the use of published information in teaching (Lemmens 2004).

Indirect control of education

There is also an indirect control of education by marketing through university-based educators who receive research funds and fees from the industry.

Guidelines (and treatment algorithms) are the most aggressive forms of marketing; they mandate prescribing with the implicit threat of possible consequences, e.g., being sued, if they are not followed.

Barry Blackwell

CorporateCorruption in the Psychopharmaceutical Industry

1. ***Overdosed America.*** **John Abramson, M.D. Harper Press. 2004.**
2. ***The Truth about Drug Companies: How they deceive us and what to do about it.*** **Marcia Angel, M.D. Random House. 2005.**
3. ***Selling Sickness.*** **Ray Moynihan and Alan Cassells. Nation Books. 2005.**
4. ***On The Take.*** **Jerome P. Kassirer, M.D. Oxford University Press, 2005.**
5. ***Law and Ethics in Biomedical Research:Regulation, conflict of Interest, Liability.*** **Trudo Lemmens and Duff Waring. University of Toronto Press. 2006.**
6. ***Our Daily Meds.*** **Melody Peterson. Picador. 2008.**

7. ***The Anatomy of an Epidemic:Magic bullets, Psychiatric drugs and the astonishing rise of mental illness in America.*** **Robert Whitaker. Crown Publishing.**

Tobreak the impasse

Blaming industry for withholding information; chastising governments for allowing the release of semi-finished products: and slanting academic psychiatry for confounding education with marketing, have little impact and might even backfire in a society in which Social Darwinism prevails, the authority of governments is in decline and the power of multinationals is in the ascendancy. There is no political solution for any of these issues, but all three issues would be resolved by the identification of the treatment-responsive form(s) of illness within the diagnostic categories and the delineation of the therapeutic profile of psychotropic drugs. Development of a pharmacologically valid psychiatric nosology would break the impasse of progress in neuropsychopharmacology and "translational research" in psychiatry and provide the pharmaceutical industry the necessary feedback to develop clinically selective drugs in mental illness.

Proposed for breaking impasse (Ban)

Composite Diagnostic Evaluation

Nosological homotyping

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