TOWARDS A CLINICAL METHODOLOGY FOR NEUROPSYCHOPHARMACOLOGICAL RESEARCH

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A NEUROPSZICHOFARMAKOLÓGIAI KUTATÁS KLINIKAI MÓDSZEREIRŐL

A neuropszichofarmakológia az elmebetegségek patofiziológiáját és kezelését tanulmányozza a központi idegrendszerre ható gyógyszerek alkalmazásával. A neuropszichofarmakológiai kutatásban a pszichotrop szerek klinikai hatásai kapcsolatban vannak a gyógyszerek agyi hatásmechanizmusával. A kutatás arra a feltételezésre épül, hogy egy klinikailag szelektíven ható gyógyszer hatásmechanizmusának tanulmányozása információt nyújt annak az elmebetegségnek vagy klinikai szindrómának a patofiziologiájáról, amelyben a gyógyszer szelektíven hatásos. Egy elmezavar patofiziologiájának ismerete viszont hasznos információt ad a farmakológusok számára újabb és hatásosabb gyógyszerek kidolgozásához. Tekintve, hogy a jelenleg forgalomban levő gyógyszerek hatásmechanizmusa farmakológiailag heterogen diagnosztikus csoportokhoz köthető, a mai kutatás nem ad sok használható információt ehhez. A jelenlegi diagnosztikai csoportok farmakológiai heterogenitásának kiküszöbölésére megpróbálták a tradicionális pszichiátriai diagnózisokat lebontani, jól körülírt neurobiológiai deficit szindrómákra, vagy a hagyományos nozológiát behelyettesíteni egy genetikus pszichiátriai nozológiával. De a pszichiátriai betegségeknek máig sincs semmilyen megfelelőbb klasszifikációja, mint a pszichopatológiai szindrómákra alapuló klinikai osztályozás. Ahogyan a neuropszichofarmakológia a neurotransmitter éra felől a genetikus korszak felé tart, úgy nő egyre az igény a farmakológiai szempontból homogén betegcsoportok felismerésére. A pszichotrop szerek elsődleges célpontja genetikusan pontosan meghatározott, és minden, farmakológiailag homogén pszichiátriai zavar vagy szindróma alkalmas egy genetikai hipotézis kialakítására. Annak felismerése, hogy a haladás a neuropszichofarmakológiában és a pszichózisok molekuláris genetikájában attól függ, hogy milyen gyorsan tudjuk a farmakológiai heterogenitást a diagnosztikus csoportokban megoldani, olyan klinikai metodológiák kidolgozásához vezetett, amelyek esetleg képesek a gyógyszerre reagáló betegség-alcsoportok felismerésére. Az egyik ilyen metodológia a CODE rendszer, egy másik a nozológiai homotipizálás. A CODE rendszer alkalmas metodológia olyan betegség-alcsoportok felismerésére, amelyek konvencionális diagnosztikai rendszerek használatával nem azonosíthatók. A nozológiai homotípusok pedig olyan egységes pszichiátriai szindrómák, amelyek a nozológiai mátrix azonos kategóriájába sorolhatók. A nozológiai mátrix empirikusan meghatározott diagnosztikus kategóriái alkalmasak a mentális és a neuronális folyamatok kapcsolatának tanulmányozására.

KULCSSZAVAK: alternatív fenotípusok, genetikai klasszifikáció, CODE rendszer, CODE-DD, neuropszichofarmakológiai kutatás, nozológiai homotipizálás, nozológiai mátrix, polaritás, pszichopatológiai tünetek, időbeli szerveződés, totalitás

SUMMARY

Neuropsychopharmacology is dedicated to the study of the pathophysiology and treatment of mental pathology with the employment of centrally acting drugs. In neuropsychopharmacological research the clinical effects of a psychotropic drug are linked to the effects of the substance on brain structures involved in its mode of action. It is assumed, that knowledge about the mode of action of a selectively effective psychotropic drug will provide clues about the pathophysiology of the illness, and conversely, that knowledge about the pathophysiology of an illness, will provide clues for developing clinically more effective psychotropic drugs. Since the currently employed clinical methodology for the

demonstration of therapeutic efficacy links the mode of action of psychotropic drugs to pharmacologically heterogeneous populations, neuropsychopharmacological research does not provide the necessary feedback for developing more effective drugs. To resolve the pharmacological heterogeneity within currently used diagnoses, attempts were made to split syndrome-based psychiatric diagnoses into discrete neurobiological deficits, and to. replace traditional psychiatric nosology by a genetic psychiatric nosology. Yet, to date, there is no alternative methodology to psychopathology-based psychiatric nosology for classifying mental pathology in a clinically relevant manner. As we are moving from the "neurotransmitter era" to a "genetic era" in neuropsychopharmacology, the need for identifying pharmacologically homogenous populations is becoming imminent. All primary targets of psychotropic drugs in the brain are encoded by genes which are identified, and any nosologic entity or psychiatric syndrome that corresponds with a treatment responsive population is a candidate for the generation of genetic hypotheses relevant to mental illness. Recognition that progress in neuropsychopharmacology, and molecular genetic research, depends on the speed clinical research can resolve the pharmacological heterogeneity within currently used diagnoses, led to the development of methodologies for the identification of treatment responsive form(s) of illness, such as the Composite Diagnostic Evaluation (CODE) System, and nosologic homotyping. The CODE System is a methodology for the identification of treatment responsive forms of illness if covered up by consensus-based diagnoses; it consists of a set of diagnostic algorithms that can assign simultaneously a diagnosis from several classifications to a patient. Nosologic homotypes are identical in elementary units of mental illness and are assigned the same position in the nosologic matrix, based on three "nosologic organizing principles. The empirically derived diagnostic categories are suitable for testing hypotheses relevant to the relationship between the "processing of mental events" and "signal transduction" in the central nervous system.

KEYWORDS: alternative phenotypes, genetic classification, CODE System, CODE-DD, neuropsychopharmacological research; nosologic homotyping, nosologic matrix; polarity, psychopathologic symptoms, temporal organization, totality

INTRODUCTION

The therapeutic and commercial success of chlorpromazine in the mid-1950s generated interest to develop drugs for psychiatric indications (Caldwell, 1970). By the end of the 1950s there were at least 22 new drugs for the treatment of different psychiatric disorders (Ban, 2001a; Ban and Ucha Udabe, 2006). With the introduction of drugs with demonstrable therapeutic efficacy pharmacotherapy was receiving a steadily increasing share in the treatment of mental illness, and psychopharmacology became part of the teaching curriculum in psychiatry.

The term, psychopharmacology, was introduced in 1920 by David Macht, an American pharmacologist, to describe the effects of drugs on psychometric performance tests (Macht, 1920). In the 1940s, with the availability of the psychotomimetic, lysergic acid diethylamide (Hofmann, 1970), research in psychopharmacology was extended to the study of model psychoses; and in the 1950s, with the rapidly growing number of psychotherapeutic drugs, it also embraced efficacy studies for the demonstration of the effectiveness of new treatments (Ban, 1996, 2004).

Simultaneously with the introduction of psychotropic drugs, there was a shift in the understanding of signal transduction in the brain from a purely electrical to a chemically mediated event; and by the end of the 1950s there were six chemical neurotransmitters identified in the central nervous system (CNS) (Ban, 2001a). Recognition of chemical mediation at the site of the synapse, coupled with the introduction of the spectrophotofluorimeter (Bowman, Caulfield and Udenfriend, 1955) – an instrument with a resolution power to measure the concentration of cerebral monoamines, such as norepinephrine and serotonin, involved in neuronal transmission at the synapse – led to the development of neuropharmacology, the discipline dedicated to the study of the mode of action of psychotropic drugs (Ban, 1996). Previously, research dealing with centrally acting drugs, was restricted to behavioral pharmacology, and neurophysiological measures (Simon, 1998).

Spectrophotofluorimetry provided direct access to the detection of the biochemical changes responsible for the clinical effects (Ban, 1999).

Developments in pharmacotherapy, psychopharmacology and neuropharmacology triggered the development of neuropsychopharmacology, a composite discipline, dedicated to the study of the pathophysiology and treatment of mental pathology with the employment of centrally acting drugs (Ban, 2004). The new discipline has grown on the premise that research on the mode of action of psychotropic drugs with well-defined, selective therapeutic indications will generate the necessary knowledge about the pathophysiology of psychiatric disorders to guide the development of more effective pharmacological treatments.

By the late 1950s, the neurotransmitter era, the first epoch in the history of neuropsychopharmacology, was in progress (Ban and Ucha Udabe, 2006).

The neurotransmitter era

In the neurotransmitter era neuropsychopharmacological research in the pathophysiology and treatment of mental illness was guided by knowledge derived from the effects of psychotropic drugs on neurotransmitter dynamics and metabolism (Pletscher, 2006); psychotropic drug development was driven by a rapidly developing technology that provided neuropharmacology with a capability to determine the regional distribution of neurotransmitters (Kety and Elkes, 1961), the effect of drugs on the release and uptake of neurotransmitters (Axelrod, Whitby, Hertting, 1961), and the affinity of drugs to neurotransmitter receptors (Snyder, Creese and Burt, 1975).

The variations in therapeutic responsiveness to the same drug in a diagnostic category focused attention on the pharmacological heterogeneity within the diagnostic groups (Ban, 1969). Yet, no attempt was made to resolve the heterogeneity by the identification of pharmacologically homogenous populations that respond selectively to one or another psychotropic drug (Ban, 1999). The difficulties, created by the pharmacological heterogeneity within the diagnostic groups for the demonstration of therapeutic efficacy, were overcome by the adoption of a statistical methodology, the randomized clinical trial (RCT).

RCTs made it possible to detect the therapeutic effects of psychotropic drugs in pharmacologically heterogeneous diagnostic populations. By providing a means for the demonstration of statistically significant superior efficacy of a psychotropic drug to an inactive placebo in a diagnostic group without the identification of the characteristics of the treatment responsive subpopulation within the diagnostic group (Ban, 2006), RCTs led to semi-finished products in the treatment of mental illness. They also deprived neropsychopharmacological research from the necessary feedback to develop clinically more selective and thereby more effective psychotropic drugs.

RCTs had a major impact on drug regulation and on the clinical use of psychotropic drugs. By accepting that a drug is effective in a particular population if statistically significantly superior to an inactive placebo with a 0.05 or greater level of probability in two pivotal studies, authorities, in the US, Canada, and some other countries, approve the use of a psychotropic drug in a diagnostic group in which only 2 of 8 patients show a favorable response to its pharmacological effects. Such a narrow difference between the active drug and placebo marginalizes the importance of pharmacological treatment and blurs the difference between pharmacological and other treatments. In the absence of the identification of the treatment responsive form of illness, the potential benefits of drugs may be compromised by their indiscriminate use (Ban, 2006; Ban and Ucha Udabe, 2006).

In neuropsychopharmacological research the effect of a psychotropic drug on mental illness is linked with the effect of the substance on brain structures involved in its mode of action (Ban, 2002). By linking the mode of action of a drug with a pharmacologically heterogeneous diagnostic population, psychopharmacologic research does not provide the necessary feedback for progress in treatment.

As we are moving forward from the neurotransmitter era to a genetic era in neuropsychopharmacology, the gap between a neuropharmacology, with the capability to tailor drugs to receptor affinities by the employment of a rapidly growing genetic technology, and a psychopharmacology, with a methodology that is capable only to demonstrate therapeutic efficacy, has become so wide that it interferes with progress in the pharmacotherapy of mental illness.

The inconsistent and conflicting findings in molecular genetic research led to a steadily growing dissatisfaction (Hyman, 1999) with consensus-based diagnoses and classifications, such as the

DSM-IV^{TM} of the American Psychiatric Association (1994), and the ICD-10 of the World Health Organization (1992). Since all the primary targets of psychotropic drugs in the brain, e.g. G-protein coupled receptors, nuclear hormonal receptors, ion channels, enzymes, etc. are encoded by genes that have been identified, any nosologic entity that corresponds with a treatment responsive population is suitable for the generation of genetic hypotheses relevant to mental illness (Ban, 2002).

Towards a genetic era

By the late 20th century the dissatisfaction with the clinical end points given in consensus-based classifications was so severe that it was proposed to re-conceptualize mental illness in terms of genetically meaningful "discrete neurobiological deficits," also referred to as "alternative phenotypes," such as the "abnormality of smooth pursuit eye movement" (Holzman et al. 1988) linked to a locus on the short arm of chromosome 6 (Arolt et al. 1996), and the "P-50 evoked response deficit" (Freedman, Adler and Leonard, 1999) linked to the α_1-nicotinic acid receptor on the long arm of chromosome 15 (Freedman et al. 1997). Nevertheless, the usefulness of these "alternative phenotypes" in biological resreach in schizophrenia is questionable because both "phenotypes" are encountered several times more frequently in the general population than schizophrenic disorders (Faraone, Tsuang and Tsuang , 1999).

It has also been suggested to replace traditional psychiatric nosology by a "genetic psychiatric nosology" which would classify patients into categories that "correspond with the genes." While such a nosology could focus attention on overlasp between certain traits, e.g. depression and anxiety, it would group together individuals who fully qualify for a particular disease and individuals who, despite carrying the genes for the disease, are symptom free (Faraone, Tsuang and Tsuang, 1999).

Recognition that to-date there is no alternative methodology to psychopathology-based psychiatric nosology for classifying mental pathology in a clinically relevant manner (Ban, 2002), stimulated interest in linear regression equations for the identification of the treatment responsive form(s) of illness within the currently used diagnoses. However, findings with linear regression analyses of rating scale scores – generated in clinical drug trials designed for the demonstration of therapeutic efficacy – were inconsistent (Ban, 1987; Roth and Barnes, 1981). Rating scales constructed for the assessment of change in the severity of psychopathology, are sensitized by the omission of psychopathological symptoms that are not influenced by treatment, or by the retention of only those symptoms that show the largest changes (Ban, 1999). While sensitized scales are eminently suited for the demonstration of the efficacy of a drug in the shortest possible time in the smallest number of patients, they preclude the possibility of findings any relevant information for the identification of treatment-responsive forms of illness by metanalyses in the data of RCTs with psychotropic drugs (Ban, 2006).

The CODE system

There are two diagnostic instruments in development to provide pharmacologically more homogenous populations for research than the diagnostic categories of consensus-based classifications: the Composite Diagnostic Evaluation (CODE) System, and Nosologic Homotyping. The CODE System is a methodology for the identification of the treatment responsive form of illness if covered up by consensus-based, or other broadly defined diagnoses. An important impetus for the development of the CODE-System was the finding of Frank Fish that the traditional diagnostic concept of schizophrenia covered up the powerful effectiveness of phenothiazine neuroleptics in a subpopulation of schizophrenia (Fish, 1964). With the employment of Karl Leonhard's classification of "endogenous psychoses," he revealed that 3 of 4 patients with unsystematic schizophrenia, one of the two classes of disease subsumed under the diagnosis of schizophrenia, responded favorably to neuroleptic phenothiazines, whereas only about 1 of 4 patients with systematic schizophrenia showed a similar favorable response . Response rate in affect-laden paraphrenia, one of the three forms of unsystematic schizophrenia was about 85%, whereas in the different forms of systematic schizophrenia, response rates were below 25% (Fish, 1964; Leonhard, 1957).

The CODE System consists of a set of diagnostic instruments ("CODES") that can provide for polydiagnostic evaluation in distinct categories of mental illness by the employment of an integrated criteria list and standardized data collection. Each CODE consists of a vocabulary, or set of variables ("codes"), that includes all the elementary units (variables) of the diagnoses in the component

classifications; a structured interview, that provides algorithms for the determination of the presence or absence of each variable; and diagnostic decision trees that provide diagnoses in all the component diagnostic systems (Ban, 1991). In addition, each CODE includes a rating scale, based on a subset of variables from the vocabulary, for the determination of the severity of the clinical state across diagnoses. A unique characteristic of the CODE System is that it provides readily accessible information relevant to the diagnostic process from the lowest to the highest level of decision-making. The first set of provisional CODEs included polydiagnostic algorithms for anxiety disorders (CODE-AD), for depressive disorders (CODE-DD), hyperthymic disorders (CODE-HD) and schizophrenic disorders (CODE-SD) (Ban, 2001b; Gaszner and Ban, 1998).

CODE-DD

The prototype of the CODE System is CODE-DD, the CODE for unipolar depressive disorders (Ban, 1989). One of the contributing factors to its development was the recognition that the diagnosis of "vital depression" was covered up in consensus-based classifications, such as the DSM-III (American Psychiatric Association, 1980). Vital depression, characterized by "corporization," "disturbance of vital balance," and the "feeling of loss of vitality" (Schneider, 1920, 1950, 1959), is the form of depression that provided Roland Kuhn, the necessary diagnostic end-point to recognize the antidepressant effect of imipramine (Kuhn, 1957). In currently used consensus-based classifications, the diagnosis of "vital depression" is covered up to the extent that even in a severely ill patient who displays all the possible symptoms and signs considered for the DSM-III, DSM-III-R and DSM-IV (American Psychiatric Association 1980, 1987, 1994) diagnoses of "major depression," and the ICD-10 (World Psychiatric Association 1992) diagnosis of "depressive episode," one still would not know whether the patient qualifies for vital depression.

CODE-DD consists of a 90-items vocabulary, a structured interview, a 40-items severity subscale, and 25 diagnostic decision trees. Of the diagnostic systems included in CODE-DD, three are based on the conceptual development of the classifications of depressive disorders in Europe (Kraepelin, 1896, 1921; Leonhard, 1957; Schneider, 1959); and three on the conceptual development of classifications in North America (Feighner et al. 1972; Robins and Guze, 1972; Spitzer, Endicott and Robins, 1978); two are consensus-based classifications, one based primarily on the consensus of experts in the USA (American Psychiatric Association, 1987), and one on the consensus of experts in Europe (World Health Organization, 1988); ten are empirically derived classifications, the result of factor or cluster analyses of psychiatric rating scales (Foulds, 1973, 1976; Hamilton and White, 1959; Lewis, 1934; Kiloh and Garside, 1963; Mendels and Cochrane, 1968; Overall et al. 1966; Paykel, 1971; Pilowsky, Levine and Boulton, 1969; Raskin and Crook, 1976; Wing, Cooper and Sartorius, 1974); six are miscellaneous classifications (Berner et al. 1983; Kielholz, 1972; , Klein, 1973, 1974; Pollitt, 1965; Taylor, 1986; Winokur, 1974, 1979); and one is a composite diagnostic classification, based on the different classifications included in CODE-DD.

One would expect low inter-rater agreement in such a complex system like CODE-DD. However, in the first reliability study that included 239 patients there was an 87.8% inter-rater agreement on the presence or absence of the 90-items of the vocabulary (Morey, 1991). In the second, inter-rater agreement increased to 100% (Ban et al. 1993). In a validation study that included 230 of patients with a clinical diagnosis of major depression, there was a 99.6% correspondence between the clinical DSM-III-R and CODE-DD diagnosis of major depression. In another validation study which included 322 patients, the correspondence was 97.2% (Ban et al, 1993). CODE-DD was translated and adopted from the English original (Ban, 1987) into Estonian (Mehilane, 1992), French (Ferrero, Crocq, and Dreyfus, 1992), Italian (Aguglia and Forti, 1989), Polish (Puzynski, Jarema and Wdowiak, 1989), and Portuguese (Nardi and Versiani, 1990). It was used in a series of clinical studies in the early development of reboxetine, a selective NE re-uptake blocker (Ban et al. 1998).

Findings with CODE-DD correspond with the commonly held view that the DSM-III-R diagnosis of major depression is a broad diagnostic category. If depressive illness were characterized by unmotivated depressed mood, depressive evaluations, and lack of reactive mood changes, from the 322 patients with the clinical diagnosis of major depression – included in the second validation study – only 119 patients, i.e. 37% would have qualified for depression. Findings with CODE-DD

are also in keeping with the notion that depression consists of more than one form of illness. From the 322 patients only 95 patents, i.e. 29.5%, fulfilled definite criteria of Kraepelin's depressive states, characterized by motor retardation, retardation of thought and difficulties of concentration (Kraepelin, 1896), and even less, 45 patients, i.e. 14%, fulfilled criteria of Schneider's vital depression (Schneider, 1920). The overlap between the two forms of depressive illness was negligible (Ban, 2001b).

CODE-UD

To extend the scope of CODE-DD for uncovering depressive diagnoses, the instrument was revised. In the revised instrument (CODE-DD-R), also referred to as CODE-UD, , the vocabulary was increased from 90 to 220 variables, and the number of diagnostic algorithms from 25 to 84, also. CODE-UD includes all major diagnostic concepts and classifications of melancholia/depression from Hippocrates (460-377 BC) to the DSM-IV (American Psychiatric Association, 1994).

The term "melancholia" was first used in the 5th century BC, in reference to all chronic mental syndromes that did not qualify for epilepsy, hysteria, or Scythian disease (transvestism), in the Works of Hippocrates (Adams, 1929). Until the late 18th century the concept of melancholia had virtually no relationship with our current concept of depression; Boissier de Sauvages classified the melancholias as disorders of intellect (Sauvages, 1769) and Willam Cullen as disorders of judgment (Cullen, 1772).

Development of our current conceptual framework relevant to depressive illness began in the early 19th century by Johann Christian Heinroth's recognition that melancholia is a disorder of affect. Heinroth (1818) perceived insanity as exaltation or depression of one of three faculties (emotion, intellect, volition) of the mind, and classified melancholia as partial insanity that is characterized by depression of emotions. (Heinroth, 1818). Twenty years later, by separating lypemania (lupos=sadness), or melancholy of the ancient (Healy, 1997) from the monomanias (intellectual, affective and instinctive), Jean-Etienne Dominique Esquirol, set the stage for a development that led to our current diagnostic concepts and classifications of depression (and also of other mental disorders) (Esquirol, 1838).

Nosologic homotyping

The need for a pharmacologically valid, empirically derived nosology was first expressed in the late 1950s by Fritz Freyhan, a German born, American psychiatrist. He recognized the differential responsiveness to the same psychotropic drug in the same (Kraepelinian) diagnostic category, and suggested a pharmacological re-evaluation of psychiatric nosology with the employment of target symptoms and diagnoses (Freyhan, 1959; Shorter, 2005).

Nosologic homotyping is a methodology for the development of an empirically derived, pharmacologically valid, classification of mental disorders. Nosologic homotypes are identical in "elementary units" of mental illness and are assigned the same position in the "nosologic matrix" constructed with the employment of nosologic organizing principles (Ban, 2002)

The elementary units of mental illness are psychopathologic symptoms; each psychopathologic symptom has a content derived from past experience, and a form, characteristic of the illness (Jaspers 1910, 1913). Each psychopathologic symptom represents a distinct pathology in the processing of mental events, and each psychopathological symptom profile, is a "phenotype" of a mental disorder. The temporal organization of the psychopathologic symptoms reflects the pathological process in its "dynamic totality," and the "dynamic totality" of the pathological process, together with the "totality" and "polarity" of the clinical picture, provides a "structure" that is determined by the illness (Ban, 1987). It is in terms of this "determining structure," that each mental illness is defined and assigned a place in the "nosologic matrix" based on three nosologic organizing principles (Ban, 2002).

The first organizing principle of psychiatric nosology is "totality," i.e. the inclusiveness of the psychopathologic process (Ban, 1970). It was the organizing principle in the classification of Cullen (1772), Esquirol (1838), Kahlbaum (1863), and many others. On the basis of "totality," insanity is divided into "universal" ("total") and "partial"; in "partial insanity," in contrast to "universal insanity," personality remains preserved. The concept of "partial insanity" was extended to include "abortive" (distinct from "true"), "selective" (distinct from "universal") and "incomplete" (distinct from "complete") mental illness (Ban, 2000). In "abortive" mental illness patients are aware (have

insight) that their thinking and/or feelings and/or actions are pathological. (Westphal, 1878); in "selective" mental illness, the pathology of mental integration is restricted to one (or two) of the three field(s) of consciousness, i.e. the external world ("allopsychic"), the self ("autopsychic"), and the body ("somatopsychic"). (Wernicke, 1899); and in "incomplete" mental illness the pathology is restricted to one or two of the three components of the "psychic reflex," i.e, afferent ("perceptual-cognitive"), central ("relational-affective"), and efferent ("motor-adaptive") (Leonhard, 1957).

The second organizing principle of psychiatric nosology is the temporal organization of the psychopathologic process, i.e. the "onset" ("sudden" vs/ "insidious"), "course" ("episodic" vs. "continuous") and "outcome" ("recovery" vs "defect"). It was the organizing principle of mental illness in the sixth edition of Kraepelin's textbook (Kraepelin, 1899), and has remained the organizing principle in the classifications of mental illness to-date. On the basis of the temporal organization of psychopathologuc symptoms "attacks," i.e. episodes that last from minutes to hours, are distinguished from "phases," i.e. episodes that last from days to years, and from "periods," i.e. "phases" that recur with regularity; and "thrusts," i.e. acute events that yield lasting changes, are distinguished from " continuous process," i.e. chronic events that yield highly differentiated irreversible "end-states," and from "progressive deterioration," i.e. chronic events that yield severe dedifferentiation terminating in irreversible dementia (Jaspers, 1913).

The third organizing principle of psychiatric nosology is the spatial organization of the psychopathologic process, i.e. "polarity" of the psychopathological process. The origin of the concept of "polarity," is in Edda Neele's evalution of phasic sicknesses diagnosed between 1938 and 1942 in Karl Kleist's "clinic" in Frankfurt (Neele, 1949; Teichmann, 1990). Polarity was to become the dominant organizing principle in Karl Leonhard's classification of endogenous psychoses in which "monopolar" ("simple") psychoses, such as the phasic psychoses and systematic schizophrenias, were separated from the "bipolar" ("multiform") psychoses, such as manic-depressive disease, the cycloid psychoses, and the unsystematic schizophrenias (Leonhard, 1957). Within Leonhard's frame of reference, bipolar illness swings between two poles of mood and/or emotions and/or motility, and displays a continuously changing, variable clinical picture, whereas "unipolar" illness is restricted to one pole of mood and/or of emotions and/or of motility, and displays the same symptomatology within and across episodes. Each form of "unipolar" illness is distinct and characterized by a syndrome associated with no other forms and not even transitionally related to any other form.

Nosologic homotypes, are more homogenous populations in terms of psychopathology than populations identified by any of the available diagnostic instruments. If nosologic homotyping would identify pharmacologically or genetically homogenous populations it would indicate that phenomenological psychopathology and psychiatric nosology could provide the key for the delineation of biologically meaningful disease categories in psychiatry. By linking the mode of action of psychotropic drugs to pharmacologically homogeneous populations, nosologic homotyping could break the impasse in progress of neuropsychopharmacological research, pharmacotherapy, and molecular genetic research in mental illness (Ban, 2002).

Furthermore, 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 transduction" 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. Thus, "nosologic homotyping" could open the path for the development of a psychiatry, in which mental pathology is perceived in terms of pathology in "signal transduction" in the brain, and, for a rational pharmacotherapy of mental illness.

Concluding remarks

Recognition of a possible relationship between drug-induced changes in psychopathology, and in the concentration of monoamine neurotransmitters and their metabolites in the brain led to the formulation of the hypothesis that the psychotropic effects of drugs are related to their action on the transmission (processing) of impulses at the synaptic cleft (Ban, 2000, 2002, 2006; Brodie, Shore and Pletscher, 1956a,b; Pletscher, Shore and Brodie, 1955, 1956; Shore, Silver and Brodie,

1955a,b). The notion that drugs exert their psychotropic effects through the modification of transmission of impulses from one neuron to another has far reaching heuristic implications for psychiatry. The cerebral cortex of the human brain contains about 10 billion neurons, with about one million billion connections, of which the majority communicates only with each other (Edelman, 1992). The lack of consistent biological manifestations in mental illness has raised the possibility that the site of mental pathology is the major compartment of the cerebral cortex that has no direct contact with either sensory input or behavioral output (Ban, 2004). If this is the case, the primary manifestations of the psychiatric disease process are psychopathological symptoms and nosologic entities, i.e. patterns of psychopathologic symptoms (Ban, 1987), and nosologic homotyping is a suitable methodology for rendering the morphologic substrate of mental pathology accessible to scientific scrutiny.

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