FROM MELANCHOLIA TO DEPRESSION
A HISTORY OF DIAGNOSIS AND TREATMENT

Thomas A. Ban

International Network for the History of Neuropsychopharmacology

2014

From Melancholia to Depression A History of Diagnosis and Treatment[1]

TABLE OF CONTENTS

INTRODUCTION

Descriptions of what we now call *melancholia* or *depression* can be found in many ancient documents including *The Old Testament, The Book of Job,* and Homer's *Iliad,* but there is virtually

[1] The text of this E-Book was prepared in 2002 for a presentation in Mexico City. The manuscript was not updated.

no reliable information on the frequency of “melancholia” until the mid-20th century (Kaplan and Saddock 1988).

Between 1938 and 1955 several reports indicated that the prevalence of depression in the general population was below 1%. Comparing these figures, as shown in table 1, with figures in the 1960s and ‘70s reveals that even the lowest figures in the psychopharmacological era (from the 1960s) are 7 to 10 times greater than the highest figures before the introduction of antidepressant drugs (Silverman 1968).

TABLE 1

AUTHOR	YEAR	%
Cohen and Fairbank	1938	0.8
Lemkau et al	1941	0.9
Lin	1952	0.4
Eaton and Weil	1955	0.9
Leighton et al	1963	7.5
Blumenthal and Dielman	1975	13.0
Vaisanen	1975	7.5
Brown et al	1977	8.0 -10.0
Brown and Harris	1978	15-17.0
Duncan-Jones and Henderson	1978	11.0
Weissman and Myers	1978	6.5

The prevalence of depression in epidemiological studies prior to (above the dotted line) and after (below the dotted line) the introduction of antidepressants. [Based on Silverman (1968) and Hoenig (1980)].

Hoenig (1980) suggests that the likely explanation for the increase in the prevalence of depression after the introduction of antidepressants is "not a tidal wave of an epidemic of

depression" but a "change in our concepts of depressive illness brought about by a widening of our experience with depression, seeing it for the first time in new (outpatient) settings".

In the mid-1990s, the life time risk for depression was estimated as 3% to 4% worldwide (Blazer et al 1994; Horvath and Weissman 1995). In the fourth edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (1999) with text revision (DSM-IVTM), the lifetime risk for "major depressive disorder", as shown in table 2, is given as 13% with a point prevalence of 4.75%; the life time risk for "bipolar disorder" as 1% (from 0.4% to 1.6%); and the lifetime risk for "dysthymic disorder" is 6% with a point prevalence of 3%.

TABLE 2

DIAGNOSES	**LIFE TIME RISK**	**POINT PREVALENCE**
MAJOR DEPRESSIVE DISORDER	13.00%	4.75%
Woman	10 - 25%	5 - 9%
Man	5 - 12%	2 - 3%
DYSTHYMIA	6.00%	3.00%
BIPOLAR DISORDER	1.00%	

Life-time risk and point prevalence figures for major depression, dysthymia and bipolar disorder. (Figures are adopted from DSM-IVTM 1999).

For several decades during the 20th century, depressive illness was perceived as a recurrent episodic disease with full remission between episodes. Today, chronic depression [major depressive disorder (MDD) chronic, dysthymic disorder, double depression, MDD in incomplete remission] accounts for an estimated 30% to 35% of all cases of depression (Keller et al 1995; Kessler et al 1994; Michalak and Lam 2002). There is a fine line between depressive illness and melancholic temperament, and as shown in table 3, depressive symptoms and clinical features are present from 6% to 43% of the people in the general population who have never qualified for a depressive diagnosis (Beck 1967; Hoenig 1980).

TABLE 3

MANIFESTATIONS	**DEPTH OF DEPRESSION**			
CLINICAL FEATURES	NONE	MILD	MODERATE	SEVERE
Stooped posture	6	32	70	98
Diurnal variation	6	13	37	37
Distorted self-image	12	33	50	66
Suicidal ideas (wishes)	12	47	73	94
Feelings of hopelessness	14	58	85	86
Loss of interest	14	56	83	92
Sadness (low mood)	16	72	94	94
Loss of appetite	17	33	61	88
Sad face	17	72	94	98
Indecisiveness	18	42	68	83
Constipation	19	26	38	52
Negative expectations	22	55	72	87
Loss of motivation	23	54	88	88
Feelings of inadequacy	25	56	75	90
Slowed speech	25	53	72	75
Feelings of guilt	27	46	64	60
Loss of libido	27	38	58	61
Crying spells	29	44	63	83
Sleep disturbance	31	55	73	88
Loss of gratification	35	65	86	92
Self-dislike	37	64	81	86
Low self-esteem	38	60	78	81
Fatigability	39	62	89	84
Self-blame	43	67	80	80

Frequency of depressive manifestations & clinical features encountered in the population with no depression and in mild, moderate and marked depression (Beck 1967, Hoenig 1980).

To control depression, the use of antidepressants has grown steadily since the late 1950s. By the late 1990s nearly 3% (1.77 million people) of the 59 million general population in the UK, and probably a higher percentage in the US, were taking one or another antidepressant for depression or for diseases assumedly on the depressive spectrum (Dawson and Tylee 2001; House 2001). This is almost 10 times the population who had required medical attention for affective disorders annually (0.3%-0.4%) prior to the introduction of antidepressant drugs (Mayer-Gross, Slater and Roth 1960). Nevertheless, in spite of the rapidly growing use of antidepressants in the Western World -- with prescriptions jumping 62% in Canada from 1996 to 2000 – depression has become the fifth leading cause of disability by the end of the 20th century, accounting for 4.2% of the World's Total Burden of Disease in Disability Adjusted Life Years (Kleinman and Cohen 2001; Pearson 2002; World Health Organization 1999). Furthermore, if current trends continue, depression caused disability is expected to become by 2020 the second (to ischemic heart disease) leading cause of disability worldwide, and the largest cause of disability in developing regions (Murray and Lopez 1997).

It has been suggested that in spite of the extensive use of antidepressants, depression is still undertreated even in the Western World --e.g., with prescriptions jumping 69% in Canada from 1996 to 2000-- because of a variety of social and educational factors from poverty to poor compliance; and there are indications that the projected increase in depression-induced disability can be curbed to some extent by increasing the use of antidepressants. In Canada for example, there was a decrease in the point prevalence of major depression (from 2.4% to 1.95) from 1994 to 1996 with the increasing proportion of persons with depression (from 18.2% to 36.6%) receiving antidepressant treatment (Patten 2002). However, considering that only 1 of 3 depressed patients responds to the pharmacological action of antidepressants, depression-induced disability could be significantly reduced only by the identification of the treatment responsive forms of illness to the different antidepressant drugs (Ban 2001).

Since there are no guidelines on how to match different forms of depression with different

forms of treatment, in the following the historical development of depressive diagnoses and treatments will be reviewed to provide orientation points for diagnosing and treating depressed patients.

DIAGNOSIS AND CLASSIFICATION OF MELANCHOLIA AND DEPRESSION

The term, melancholia (black bile), first appeared in the Corpus Hippocraticum (460 to 370 BC). It was used in reference to all chronic mental disturbances which did not qualify for epilepsy, hysteria, or Scythian disease, referred to as transvestism in our current terminology (Adams 1929).

The association between sadness and melancholia can be traced to the first century in Celsus' (1935) treatise, De Medicina. It was also in the first century that Aretaeus recognized that mania, i.e., acute mental disturbance without fever, can be episodic and recurrent, that melancholia, i.e., long lasting sadness, can be short lived, and that mania and melancholia may follow each other in the same patient (Menninger, Mayman and Pruyser 1968). Yet, it was only about four century later, in the fifth century, that Caelius Aurelianus (1950) characterized melancholia as "mental anguish and distress with dejection, silence, animosity, longing for death, suspicion and weeping".

FROM GALEN TO ROBERT BURTON

Galen (129-199) revised ancient “humoral theory” of insanity by combining Hippocrates' ideas about the four humors with Pythagorean theory of the four elements, and his own conception of the spirit (pneuma), into a tightly organized system based on Aristotelian logic (Healy 1997). Yet, irrespective of speculations, he recognized that "symptoms follow disease as shadow its substance", and separated melancholia, the illness, (black bile melancholia), from melancholic temperament (yellow bile melancholia). He also divided melancholia into general melancholia, brain melancholia, and hypochondriacal melancholia (Garrison 1929). For Galen, in variance to prior authorities, the cause (etiology) of melancholia was not restricted to black bile, but included also yellow bile, dietary deficiency, suppression of hemorrhoidal or menstrual flow, and emotional factors.

The first treatise *On Melancholy* was allegedly written by Galen, but some historians argue that it was compiled at a later date. Regardless, for well over 1000 years through the middle-ages, and well into the renaissance, Galen's conceptual framework dominated the understanding of melancholia (Menninger, Mayman and Pruyser 1968).

Galen's distinction between black bile melancholia and "yellow bile melancholia" was further elaborated in the 6th century by Alexander of Tralles, who characterized patients with black bile melancholia, as sad and fearful, and with yellow bile melancholia, as angry and agitated (Brunet 1933). His "humoral" etiology of melancholia was passed through the work of Avicenna (937-1037) to Timothy Bright (1586), who divided melancholia into natural melancholia, he attributed to black bile, and unnatural melancholia, he attributed to a disharmony of humors. In Bright's (1586) *Treatise of Melancholia*, natural melancholia was one of the Galenic temperaments, characterized by a sad and gloomy disposition with "a vague feeling of sullenness, irritability, moodiness, and oddities of conduct", whereas unnatural melancholia was a severe mental disorder characterized by "violent and disorderly passions" and insanity. Galen's trichotomy of melancholia was adopted into the classifications of insanity proposed by Paul of Aegina (625-700) in the 7th century, by Jean Fernel (1497-1558) in the 16th, and ultimately by Robert Burton (1621) in the 17th. Burton, in his *Anatomy of Melancholia* divided melancholia into head melancholia, body melancholia, and hypochondriacal or windy melancholia" (Menninger, Mayman and Pruyser 1968).

FROM BOISSIER DE SAUVAGES TO KARL KAHLBAUM

Sydenham's (1624-1663) shift in emphasis from symptoms to disease in the 17th century opened the path for a new era in the understanding and classification of insanity (Faber 1923). Francois Boissier de Sauvages (1768), one of Sydenham's followers, was first to undertake the task of classifying diseases, including the insanities. Melancholia (Genus 19), in Sauvages' "nosology" was assigned to the disturbances of intellectual life (Order 3 in Class 8), and, as shown in table 4, divided into 14 species' of disease.

TABLE 4

Ordinary Melancholia

Erotomania

Religious Melancholia

Imaginary Melancholia

Extravagant Melancholia

Melancholia Attonita

(characterized by immobility and silence)

Vagabond Melancholia

(characterized by an intense need of movement)

Dancing Melancholia

Hippanthropic Melancholia

(characterized by delusions of being transformed into a horse),

Scythan Melancholia

Melancholia Anglica

(characterized by wish for dying)

Zoanthropic Melancholia

(characterized by delusions of being transformed into an animal)

Enthusiastic Melancholia

(characterized by the belief of being divine)

Sorrowful Melancholia

The 14 different "species of disease", subsumed under melancholia in Boissier de Sauvages' (1768) “nosology”.

An alternative “nosology” to Sauvages was proposed soon after by William Cullen (1769), who assigned melancholia (Genus 66) to the vesanias, i.e., "disorders of judgment without pyrexia", one of the three orders of the neuroses (morbus menti). He perceived melancholia, as a “partial

madness", distinct from mania (Genus 67), i.e., "universal (total) madness", and from "amentia", i.e., a form of madness in which people "do not perceive, or do not remember the relations between things"; and divided melancholia, as shown in table 5, on the basis of the "different subjects of the patient's ravings", into eight species' of disease.

TABLE 5

Imagination that One's Body is in a Dangerous Condition
or that
One's Affairs Are in a Desperate State

Imagination that One's Affairs Are in a Prosperous State

Violent Love

Superstitious Fear of Future

Aversion from Motion and From All Offices of Life

Restlessness and Impatience

Weariness of Life

Deception Concerning the Nature of One's Species

The eight different "species of disease", subsumed under melancholia, in William Cullen's "nosology".

Cullen's (1769) "nosology" was simplified and adopted by Vincenzo Chiarugi (1793-1794), who divided melancholia into true melancholia, characterized by "constant sadness or depression of spirit", false melancholia, characterized by "imaginary happiness or elation due to erroneous ideas", and furious melancholia, characterized by "hatred and violence" against one's self or others.

The roots of Philippe Pinel's (1798) classification were also in Cullen's (1769) "nosology". Pinel (1801) divided insanity into amentia, mania and melancholia; separated idiotism from dementia within amentia; mania with delirium from mania without delirium within "mania"; and defined melancholia as "delirium about one subject exclusively".

Cullen's division between "partial" and "universal madness" was further elaborated in 1818 by Johann Christian Heinroth in his *Psychic Life and Its Disturbances.* Simulated by Thomas Reid's (1764) "faculty psychology", Heinroth (1818) conceptualized mental illness as "exaltation" or "depression" of one or another "faculty of the mind", i.e., intellect, emotion, or volition. He perceived melancholia", as a "partial insanity", a "depression of emotion", without depression of the other faculties, and distinguished between melancholia and delusional melancholia, another "partial insanity" with "mixed exaltation and depression of emotions". Heinroth's contributions, led to the re-conceptualization of "partial insanity" and to the adoption of the term "depression" for a category if illness that included "melancholia".

Heinroth's (1818) concept of partial insanity was adopted by Jean-Dominique-Etienne Esquirol (1820, 1838), a disciple of Pinel. He modified Pinel's (1801) classification, as shown in table 6, by replacing "melancholia or delirium upon one subject exclusively" with lypemania (lupos=sadness) or melancholy of the ancient, and the diagnosis of mania without delirium with monomania; by separating monomania from mania; and by dividing monomania into intellectual, affective, and instinctual. His separation of lypemania, defined as "delirium with respect to one or a small number of objects with the predominance of a sorrowful and depressing passion", from the monomanias, led to the separation of melancholia in which sad (dysthymic) mood, affects thinking, emotions and will, from all other depressions included in affective monomania.

TABLE 6

Class of Illness

Pinel	***Esquirol***
melancholia	lypemania
mania without delirium	monomania
	intellectual
	affective
	instinctual
mania with delirium	mania

dementia	dementia
idiotism	imbecility and idiocy

Corresponding classes of disease in Pinel's and in Esquirol's classifications.

Esquirol's (1838) distinction between monomania (“partial insanity”) and mania (total insanity) was retained throughout the 19th century.

The distinction between total insanity and partial insanity was also adopted by Karl Kahlbaum (1863) in his classification. Kahlbaum replaced the term melancholia with the term dysthymia, and assigned genus dysthymia melaena, a disease with the "predominance of sad emotions", to the vecordias, which in his classification, referred to the partial insanities, and included also the different forms of paranoia, i.e., genus paranoia ascensa, genus paranoia descensa, genus paranoia immota.

FROM EMIL KRAEPELIN TO KARL LEONHARD

Heinroth's (1818) influence was still detectable in the early classifications of Kraepelin (1883), who, in the first edition of his textbook, published in 1883, as shown in table 7, recognized four different forms of melancholia, from which two, melancholia simplex and delusional melancholia, were classified as mental depression; one, melancholia activa, as mental excitement, and one, periodic melancholia, as periodic psychosis. In the second edition of his text, published in 1887, melancholia was 1 of 12 classes of illness displayed in three forms, i.e., melancholia activa, melancholia simplex, and melancholia attonita. In the same edition, periodic melancholia was included in periodic and circular insanity and delusional melancholia in the class of delusional psychoses (Wahnsinn). The concept of melancholia remained unchanged in the third edition, published in 1889. It was in the fourth edition, published in 1891, that the unitary concept of melancholia, an illness characterized by retardation of movements and thoughts, was proposed. In the fifth and sixth editions, published in 1896 and 1899, respectively, melancholia was recognized

only as one of the involutional syndromes; and by the time of the seventh and eighth editions, published in 1904 and 1913, melancholia and depressive states were engulfed in the all embracing diagnostic concept of manic depressive psychosis (insanity).

TABLE 7

EDITION	YEAR	CLASSIFICATION
1st	1883	Mental Depressions : Melancholia Simplex Delusional Melancholia Mental Excitements : Melancholia Activa Periodic Psychoses : Periodic Melancholia
2nd	1887	Melancholia : Melancholia Activa Melancholia Simplex Melancholia Attonita Periodic Psychoses : Periodic Melancholia Delusional Psychoses Delusional Melancholia
3rd	1889	Melancholia : Melancholia Activa Melancholia Simplex Melancholia Attonita Periodic Psychoses Periodic Melancholia Delusional Psychoses :

		Delusional Melancholia
4th	1891	Melancholia :
		Periodic Psychoses
		Depressive Form
		Delusional Psychoses :
		Depressive Form
5th	1896	Periodic Psychoses
		Depressive form
		Involutional Psychoses
		Involutional Melancholia
6th	1899	Manic-depressive Insanity
		Depressive States
		Involutional Psychoses
		Involutional Melancholia
7th	1904	Manic-depressive Insanity
8th	1913	Manic-depressive Insanity

The place of melancholia in the classifications of Kraepelin from the 1st to the 8th edition of his textbook

Kraepelin's (1891) unitary concept of melancholia was endorsed in the United Kingdom by Mapother (1926) and received further substantiation by Lewis (1934). Nevertheless, as shown in table 8, the "unitary concept of melancholia" was broken by factor and cluster analytic studies during the 1960s and '70s into two to four distinct depressive syndromes, including agitated, anxious, dysthymic, endogenous, hostile, neurotic, and psychotic.

TABLE 8

AUTHOR	YEAR	SYNDROMES

Hamilton & White	1959	Retarded
		Agitated
Kiloh & Garside	1963	Endogenous
		Neurotic
Pilowsky et al	1969	Endogenous
		Neurotic
Foulds	1976	Psychotic
		Neurotic
		Dysthymic
Overall et al	1966	Anxious
		Hostile
		Retarded
Wing et al	1974	Psychotic
		Retarded
		Neurotic
Paykel	1971	Psychotic
		Anxious
		Hostile
		Young with personality disorder
Raskin et al	1976	Agitated
		Neurotic
		Endogenous depression
		Poor premorbid personality

Depressive syndromes derived by factor and cluster analyses

In terms of conceptual development, as shown in table 9, Kraepelin's “unitary concept of depression”, restricted originally to "endogenous depression" (Moebius 1893), was broadened first

to include “symptomatic depression”, intrinsically linked to somatic illness (Bonhoeffer 1910), and psychogenic depression, precipitated by life events (Wimmer 1916). Then, it was replaced by Kurt Schneider's (1920, 1958) trichotomy of “vital depression”, “depressive psychopathy”, an anomaly of personality development (similar to Galen's “depressive temperament”), and “reactive (psychogenic) depression”. Finally, in the 1950s, Karl Leonhard (1957) split endogenous depression into “bipolar depression”, displayed in multiform, continuously changing manifestations within and across episodes, and “unipolar (monopolar) depressions”, displayed in simple, fixed symptomatology that returns in a periodic course unchanged; and divided “unipolar depression” into “pure melancholia” [similar to Esquirol's (1838) “lypemania”] in which the dysthymic mood affects thinking, emotions and will, and five distinct forms of pure depressions, i.e., “non-participatory”, “harried”, “hypochondriacal”, “self-torturing”, and “suspicious” [similar to Esquirol's (1838) “monomanias”] in which only one or two components of the mental apparatus are diseased.

TABLE 9

KRAEPELIN'S UNITARY CONCEPT OF DEPRESSION
1889

SYMPTOMATIC	ENDOGENOUS	PSYCHOGENIC
Depression	Depression	Depression
Bonnhoeffer	Moebius	Wimmer
1910	1900	1916

SCHNEIDER (1920, 1958)

Depressive	VITAL	REACTIVE
PSYCHOPATHY	Depression	Depression

LEONHARD (1957)

Endogenous Psychoses

UNIPOLAR		BIPOLAR
Depressions		Depression
Pure Melancholia	*Pure Depressions*	
	non-participatory depression	
	harried depression	
	hypochondriacal depression	
	self-torturing depression	
	suspicious depression	

European development in the differentiation of depression

There was also a shift in emphasis regarding the cardinal symptoms of depressive illness in the different classifications, from thought retardation and decreased drive in Kraepelin's (1899), through corporisation and the feeling of loss of vitality in Schneider's 1920, to diurnal variations and sleep disturbance in Berner and his associates' (1983).

FROM ADOLF MEYER TO THE DSM-IV

Kraepelin's (1899) unitary concept of melancholia was, by and large dismissed by Adolf Meyer (1908) in the United States. He proposed a spectrum of affective reactions; replaced the term melancholia with the term depression, i.e., "depression of mental energies" (Healy 1997); and assigned, in his classification, the depressions to the "hypothermergasias" (Billings 1939). During his tenure, American psychiatry became isolated from European influence and remained isolated until Eli Robins at Washington University introduced what was to be referred to as a neo-Kraepelinan approach to the diagnosis and classification of psychiatric disorders. In keeping with

Kraepelin's unitary concept of depression, in 1972, Robins in collaboration with Samuel Guze identified one core syndrome for depressive illness, and introduced the terms "primary depression" and "secondary depression" to indicate whether the syndrome would qualify for what in Europe at the time would have been referred to as "endogenous (primary) depression" and "symptomatic (secondary) depression".

Robins and Guze's (1972) diagnostic concept of depression was further elaborated and adopted by Feighner, Robins, Guze,Woodruff, Winokur and Munoz (1972) in their Diagnostic Criteria for Use in Psychiatric Research, in which, in addition to the "primary" and "secondary " distinction, it was also defined to what extent, definitely or probably, a patient fulfilled diagnostic criteria. Then, the "Feighner Criteria" were further elaborated and adopted in the late 1970s by Spitzer, Endicott and Robins (1978) into the Research Diagnostic Criteria in which the terms "major depression" and "minor depression" that was to be adopted into the DSM-III, the first widely used consensus-based classification, first appeared (American Psychiatric Association 1980).

There are two major consensus-based classifications of mental disorders today: the International Classifications of Diseases (CD) of the World Health Organization (WHO), and the Diagnostic and Statistical Manual (DSM) of the American Psychiatric Association (APA). They were developed independently, but converged in the late 1960s with only minor differences between the DSM-II (APA 1968) and ICD-8 (WHO 1969). In both, depressive disorders were assigned to 1 of 4 diagnoses: involutional melancholia (Kraepelin 1896), manic-depressive psychosis, depressed type (Kraepelin 1899), reactive depressive psychoses (Wimmer 1916), and depressive neurosis. By the time of the publications of the ICD-10 (WHO 1993) and the DSM-IV (APA 1994), these diagnoses became history and were replaced by a unitary concept of depression that consists of one core syndrome referred to as depressive episode in the ICD-10, and major depression in the DSM-IV (Table 10), displayed with consideration of five "specifiers" in the ICD-10, and 15 "specifiers" in the DSM-IV (Table 11).

TABLE 10

ICD-10	*DSM-IV*
DEPRESSED MOOD	DEPRESSED MOOD
LOSS OF INTEREST/ENJOYMENT	LOSS OF INTEREST/PLEASURE
INCREASED FATIGUABILITY	fatigue/loss of energy
reduced concentration/attention	disturbance of thinking/concentration
reduced self-esteem/self-confidence	
ideas of guilt/unworthiness	ideas of guilt/worthlessness
bleak/pessimistic views of the future	
ideas/acts of self-harm/ suicide	thoughts of death/suicide
disturbed sleep	insomnia/hypersomnia
diminished appetite	weight loss/gain
	agitation/retardation

To qualify for depressive episode in ICD-10 at least 2 of the 3 typical symptoms (in capitals) and 2 or more of the other 7 symptoms must be present; to qualify for major depression in DSM-IV, 5 or more of the 9 symptoms must be present including at least 1 of the 2 typical symptoms

TABLE 11

ICD-10	*DSM-IV*
Mild	Mild
Moderate	Moderate
Severe without psychotic symptoms	Severe without psychotic features
Sever with psychotic symptoms	Severe with psychotic features
Recurrent	In partial remission
In full remission	

Chronic

With catatonic features

With melancholic features

With atypical features

With postpartum onset

With full inter-episode recovery

Without full inter-episode recovery

With seasonal pattern

With rapid cycling

The five "specifiers" of depressive episode in the ICD-10; and the 15 "specifiers" of major depression in the DSM-IV.

Depressive episode and major depression differ from dysthymia (the only other depressive diagnosis) in both classifications, in terms of severity and duration, with dysthymia being more prolonged, and depressive episode and major depression more severe. The diagnoses of depressive episode and major depression are sufficiently broad that they are eminently suited to include widely different conceptualizations of depressive illness. Yet, they are consensus based diagnoses, which cover up some prototype-based diagnoses. The diagnosis of vital depression (Schneider 1920), the diagnosis that made it possible for Kuhn (1957, 2002) to recognize the antidepressant effect of imipramine in a limited number of patients, is covered up in both diagnoses to the extent, that even if the patient is so severely ill that he/she displays all the possible symptoms and signs considered for the ICD-10 diagnosis of depressive episode and the DSM-IV diagnosis of major depression, one still would not know whether the patient qualifies for vital depression (Ban 2000).

TREATMENT OF MELANCHOLIA AND DEPRESSION

Treatment of melancholia through the millennia was in-keeping with contemporary beliefs. Until the 19th century there was little documentation of results.

In 1813, Samuel Tuke reported an about 70% response rate with a 65% full recovery in 30 patients with melancholia treated, without time frame defined, with combined medical and moral treatment, i.e., warm bath and bodily exercise, at the York Retreat in England (Ban 1981; Hunter and Macalpine 1964). Combined medical and moral treatment of depression and especially of chronic depression has continued as of to-date with in the 1960s antidepressants replacing warm bath, and psychotherapy, bodily exercise.. With some of the combined treatments employed around the turn from the second to the third millennium response rates were ranging from 71% (sertraline and cognitive therapy) to 85% (nefazodone and cognitive behavioral analysis system of therapy), with consistently higher response rates with the combination, than with any of the component treatments alone (Keller et al 2000; Ravindran et al 1999).

FROM OPIUM TO CHLORPROMAZINE

The roots of pharmacotherapy, the dominant treatment modality of depression after the 1960s, are in poppy, or papaver somniforum which has been used for thousands of years to relieve pain and sorrow without knowing what was responsible for its soothing effect.

In the early 16th century, Paracelsus (Aureolus Theophrastus Bombastus von Hohenheim 1493-1541) prepared an elixir (arcanum), he referred to as Laudanum, that contained the active ingredient of the plant (Ban 2001). About 200 years later, in the mid-18th century, Albrecht von Haller (1708-1777) recognized that opium was responsible for poppy's analgesic action and therapeutic effect in melancholia (Garrison 1960).

Opium in the form of a tincture was introduced in the treatment of melancholia towards the end of the 19th century by Kraepelin (1891). An opium cure was a three weeks procedure during which the dose of the substance was raised by daily increments from 3 to 25 minims, and then decreased gradually until discontinued (Nyirö 1962). It was estimated that about 50% of the patients were discharged from the hospital at the time or soon after completion of treatment. Alternative treatments included dinitrile succinate (Gillis and Salfield 1953), hematoporphyrin, a photosensitizing substance (Bruel 1957) and, in the 1950s, reserpine, the active ingredient of the snakeroot plant, that was found to alleviate anxiety and depression when used in small doses inthe

treatment of neuroses (Davies and Shepherd 1955). The use of reserpine in depression was short lived after it became recognized that it induced dysphoria in some patients when used in the treatment of hypertension (Lewis 1971).

In the mid-1950s chlorpromazine was introduced in the treatment of agitated, delusional, and involutional depression. Subsequently, antipsychotics with relatively high central anticholinergic properties, such as thioridazine (Overall et al 1966) and levomepromazine/methotrimeprazine (Ban and Schwarz 1963) were the primary pharmacological treatments of depression with psychotic features.

With the introduction of iproniazid (Crane 1957; Loomers et al 1957) and imipramine (Kuhn 1957) in 1957, the use of opium and its alternatives was promptly abandoned. Iproniazid and imipramine became the prototypes of the two major classes of antidepressants: the monoamine oxidase inhibitors (MAOIs) and the monoamine re-uptake inhibitors (MAUIs) (Ban 1981). The first series of MAUIs were "tricyclic antidepressants".

MONOAMINE OXIDASE INHIBITORS

Cerebral monoamines are derived by hydroxylation and decarboxylation from essential amino acids, e.g., norepinephrine (NE) from phenylalanine, serotonin (5-HT) from tryptophan. The enzyme, monoamine oxidase (MAO), responsible for the oxidative deamination of monoamines implicated in synaptic events, was identified in 1937 by Pugh and Quastel and by Blaschko et al independently. The MAO inhibiting effect of iproniazid, the isopropyl derivative of isoniazid, a substance used in the treatment of tuberculosis, was detected in 1952 by Zeller et al., at the University of Chicago.

Employment of the spectrophotofluorimeter rendered the detection of changes in cerebral monoamine levels accessible to direct investigation. While studying monoamine turnover in the mid-1950s, it was revealed that administration of reserpine decreased, whereas administration of iproniazid increased brain 5-HT (Besendorf and Pletscher 1956) and NE (Carlsson 1998) levels. Considering the euphoria encountered in some tubercular patients in the course of treatment with iproniazid (Selikoff, Robitzek and Orenstein 1952) and the dysphoria in some hypertensive patients

in the course of treatment with reserpine (Hollister 1998), the possibility was raised that MAO inhibition with the resulting increase of brain 5-HT and NE was responsible for the "euphorising" effect of iproniazid. Supportive of the relationship between the MAO inhibiting and euphorizing effects of iproniazid were reports, in 1957 on the effectiveness of the substance in the treatment of some depressed patients (Crane 1957; Loomers et al 1957). At variance with the relationship between MAO inhibiting and antidepressant effect were reports on the effectiveness of isoniazid, the parent substance of iproniazid, which has virtually no MAO inhibiting property, in some depressed patients (Delay et al 1952; Healy 1997; Salzer and Lurie 1953).

In spite of the tenuous evidence that MAO inhibition is responsible for the antidepressant effect of iponiazid, a series of MAOI inhibitors, including isocarboxazid, nialamide, mebanazine, phenelzine and pheniprazine, were introduced in rapid succession for the treatment of depression. For a short period of time it appeared that MAOIs would become the prevailing treatment modality of depression (Rees 1960). By the mid-1960s, however, the situation had changed. Just as rapidly as their ascent, the use of MAOIs fell from grace. First iproniazid, than pheniprazine, had to be withdrawn from clinical use because of hepatotoxicity, and after the introduction of tranylcypromine, the frequent incidence of hypertensive crises, i.e., tyramine-cheese reactions (Blackwell 1963), focused attention on potential drug-drug interaction and the need for dietary precautions in the course of treatment with MAOIs. The use of MAOIs became gradually restricted to atypical depression, i.e., depression with hysteroid features, hypersomnia, excessive appetite, etc. (Ban 1981; Sargant 1961).

The descent of MAOIs could not be reversed by the development of selective and reversible inhibitors of the type A (Youdim 1967) or the type B (Knoll 1998) isoenzymes, i.e., clorgylene and deprenyl respectively. Today, in 2002, only three MAOIs, phenelzine, a nonselective hydrazine, tranylcypromine, a nonselective phenylcyclopropylamine, and moclobemide, a selective type A inhibitor with a benzamid structure, are available for clinical use in the treatment of depression in Canada.

MONOAMINE RE-UPTAKE INHIBITORS

While the use of MAOI antidepressants after an early rise rapidly declined, the use of MAUIs steadily grew in spite of the long-time (approximately eight years) required to demonstrate the therapeutic effectiveness of imipramine, the prototype MAUI, by Klerman and Cole (1965). Their report was based on a pooled analysis of data from 23 studies with a total of 1009 depressed patients treated with imipramine (550 patients) or administered placebo (459 patients). The evidence for the antidepressant effect of imipramine was derived from the 34% higher, 65% improvement rate with the substance against the 31% improvement rate with placebo (Ban 1974). These findings imply that 2 of three patients included in those studies had a favorable response, but only in 1 of the 2 patients could one definitely attribute the favorable effects to the pharmacological action of the drug.

Early research with imipramine brought to attention its multiple pharmacological actions, i.e., antihistaminic, anticholinergic, noradrenergic and serotonergic (Domenjoz and Theobold 1959), without offering any clues which of these actions are related to its antidepressant effect. Searching for a lead, it was found that in the rat imipramine antagonized and reversed the reserpine-induced sedation, hypothermia, ptosis, and diarrhea. Since the pharmacological action of reserpine is not restricted to the depletion of NE and 5-HT, but also includes cholinomimetic effects, the effect of imipramine on reserpine-induced behavior has not contributed to the disentangling of the action mechanism of the substance. Yet, it provided a means (a test) which had been in use for decades in the pharmacological screening for imipramine-like drugs (Costa et al 1960).

Employment of the reserpine reversal test triggered research that led to the isolation of desipramine, the demethylated metabolite of imipramine, and the demonstration of its efficacy in the treatment of depression. The postulation that the antidepressant effect of desipramine is mediated by NE is based on findings that desipramine's reserpine reversal is suspended in animals selectively depleted of catecholamines by the administration of alpha-methylparatyrosine (AMPT), a selective tyrosine hydroxylase inhibitor (Brodie, Bickel and Sulser 1961; Sulser, Watts and Brodie 1962). The confounding of reserpine-reversal with antidepressant effect was compounded by the confounding of the action mechanism of the drug with the pathomechanism of the illness. The

belief that depression is the result of chemical imbalance in which NE deficiency plays a pivotal role, has not been corrected by the demonstration that administration of AMPT did not yield relapse in patients successfully treated with imipramine (Shopsin, Gershon, Goldstein, et al. 1975). It has persisted in spite of any indication that selective NE reuptake blockers would be superior to other antidepressants in the treatment of depression (Ban 1974, 1981).

The shift from selective norepinephrine (noradrenaline) reuptake inhibitors (NARI) to selective serotonin reuptake inhibitors (SSRI) began in the mid-1970s with the demonstration that an intact 5-HT system is an essential prerequisite for ß-adrenergic-receptor down regulation (Vetulani et al 1975) that results from NE re-uptake inhibition, and seemed to be a prerequisite for antidepressant effect. It culminated, in 1980, with the recognition of the correspondence between imipramine binding sites and 5-HT binding sites in the human platelet (Paul et al 1980) and in the hypothalamus of the rat (Langer et al 1980). The shift was also supported by clinical pharmacological findings which indicated that administration of parachlorophenylalanine, a 5-HT synthesis inhibitor, produced relapse in depressed patients successfully treated with antidepressants (Shopsin, Friedman and Gershon et al 1976).

By the early 1990s, the SSRIs dominated the antidepressant scene. But in spite of their unprecedented marketing success, it was recognized that SSRIs could produce insomnia, reduce appetite, interfere with sexual functioning, and might even induce irritability, anxiety (Klein 2000), akathisia, and questionably suicidal and homicidal behavior (Healy 2002). To relieve the side effects created by the stimulation of 5-HT_{2A} receptors and the inhibitory effect of serotonergic input to the dopaminergic pathways in the basal ganglia (Gill, Devane, Risch 1997; Walker 2002), a series of new antidepressants emerged in the 1990s. One of the first was venlafaxine, a nonselective but prevailingly 5-HT reuptake inhibitor (SNRI-SE), the mirror image of imipramine, and one of the last was reboxetine, a NARI. Other drugs of the new series included nefazodone, a 5-HT selective agent (SeSSA), pharmacologically related to trazodone, which blocks 5-HT_2 and has week inhibiting effect on 5-HT reuptake, and mirtazepine, a noradrenaline and serotonin selective agent (NaSSE), pharmacologically related to mianserin and trimepramine, which has no effect on 5HT reuptake (Ban 1999).

ANTIDEPRESSANTS IN CLINICAL USE (Canada)

At present, in the early years of the 21st century, as shown in table 10, there are 22 antidepressants available for clinical use in Canada: six nonselective re-uptake inhibitors including four prevailingly NE re-uptake blockers (SNRI-NA), and two prevailingly 5-HT re-uptake blockers (SNRI-SE); four selective NE re-uptake blockers (NARI); four selective 5-HT re-uptake blockers (SSRI); two noradrenergic and 5-HT selective agents (NaSSA); two serotonergic and 5-HT selective agents (SeSSA); two nonselective monoamine oxidase inhibitors (MAOI); one selective type A MAO inhibitor (MAOI-A); one NE and dopamine (DA) reuptake inhibitor (NDRI); and one serotonin precursor (SePr). There are also two natural products with demonstrated therapeutic efficacy: St.John's wort and S-adenosyl-methionine (Whitaker 2002).

TABLE 12

PHARMACOLOGICAL CLASS	***DRUGS***
SNRI-NA	Amitriptyline
	Amoxapine
	Doxepin
	Imipramine
SNRI-SE	Clomipramine
	Venlafaxine
NARI	Desipramine
	Maprotiline
	Nortriptyline
SSRI	Fluoxetine
	Fluvoxamine
	Paroxetine
	Sertraline
NaSSA	Mirtazepine
	Trimepramine

SeSSA	Nefazodone
	Trazodone
MAOI	Phenelzine
	Tranylcypromine
MAOI-A	Moclobemide
NDRI	Bupropion
SePr	L'tryptophan

The 22 drugs identified by generic name and pharmacologic class available in Canada for clinical use in 2002.

All antidepressants in clinical use in Canada have demonstrated therapeutic efficacy in at least two clinical trials. They were shown to be different from an inactive placebo with a statistically significant probability, in the treatment of major depression in at least in two pivotal studies.

Antidepressants approved for clinical use in Canada, as in the United States are not necessarily different with a statistically significant probability from placebo in all clinical studies. Khan, Khan and Brown (2002) found that in fewer than half (48%, 45/93) of the antidepressant studies, were the drugs different with a statistically significant probabilty from placebo in 52 clinical trials with 8 antidepressants (bupropion, citalopram, fluoxetine, mirtazepine, nefazodone, paroxetine, sertraline, venlafaxine) approved by the US Food and Drug Administration for clinical use between 1985 and 2000.

In spite of their structural and pharmacological difference, none of the newer drugs are better (superior) than imipramine or any of the other antidepressants in their therapeutic efficacy. As shown in table 13, response rates in in the meta-analyses of Davis et al's (1993) (which included 10 of the 22 drugs available for clinical use in Canada), ranged from 45% (paroxetine) to 79% (sertraline) with active drugs, and from 23% to 48% with inactive placebos. Response rates with two of the 10 drugs (amoxapine and fluvoxamine) were comparable to imipramine, with one (sertraline) it was higher than with imipramine, with four (phenelzine, moclobemide, fluoxetine,

amitriptyline) slightly lower than with imipramine, and with two (mirtazepine and paroxetine) markedly lower than with imipramine. Considering, however, the almost linear relationship between placebo and drug response, it is reasonable to assume that population differences accounted for the differences in response rates between the drugs. Nevertheless one may argue that with some of the newer non-tricyclic drugs, e.g., mirtazepine and paroxetine, one can no longer expect that 2 of 3 depressed patients will respond to treatment. This, of course, does not preclude the possibility that both of these drugs have the potential to help some patients in whom other antidepressants have failed.

TABLE 13

DRUGS		***RESPONSE RATES %***	
NAME	CLASS	DRUG	PLACEBO
Sertraline	SSRI	79	48
Imipramine	NSRI-NA	68	40
Fluvoxamine	SSRI	67	39
Amoxapine	NSRI-NA	67	49
Phenelzine	MAOI	64	30
Moclobemide	MAOI-A	64	24
Fluoxetine	SSRI	60	33
Amitriptyline	NSRI-NA	60	25
Mirtazepine	NaSSA	48	20
Paroxetine	SSRI	45	23

Response rates: measured by a 50% or greater decrease in the total scores of the Hamilton Rating Scale for Depression. Based on the meta-analyses of Davis et al (1993).

It has been suggested that the newer drugs have fewer side effects than first generation antidepressants. While this is not necessarily the case, SSRIs, as shown in table 14, have a different side effect profile from tricyclic antidepressants (Trindade et al 1998). They are also better tolerated, because they produce fewer anticholinergic side effects. However, if the depressions are diseases with cholinergic dominance (Janowsky 2000; Janowsky et al 1974), and central

anticholinergic receptor blockade is an essential feature in the action mechanism of antidepressants (Selbach 1959), the lower overall therapeutic response rates encountered in the meta-analyses with some of the newer drugs, and especially with the SSRIs, might be explained.

TABLE 14

SIDE EFFECTS	EVENT RATE	
	SSRI	TCA
	%	%
Agitation	14	8
Anxiety	13	7
Constipation	10	22
Diarrhea	13	5
Dizziness	13	23
Dry mouth	21	55
Headache	17	14
Insomnia	12	7
Nausea	22	12
Nervousness	15	11

Side effect profile of SSRIs and tricyclic antidepressants (TCA). Based on Trindade et al. 1998.

Each of the drugs listed in table 12 has its own identity with a distinct chemical structure, pharmacological action and side effect profile. There is virtually no information on the therapeutic profile of antidepressants. The only indication for a possible difference in the therapeutic profile of antidepressants drugs is the clinical finding that responsiveness in treatment refractory patients to a second, structurally and pharmacologically different antidepressant, is encountered more frequently than it could be accounted for by chance (Ban 1999).

CLINICAL PSYCHOPHARMACOLOGY OF ANTIDEPRESSANTS

Pharmacotherapy with antidepressants focused attention on the pharmacological heterogeneity of depressive illness, but attempts to resolve the heterogeneity by the identification of the treatment responsive form(s) of illness by linear regression equations, biological markers, pharmacological load tests and/or biochemical indicators yielded inconsistent results (Ban 1969, 1974, 1981, 1987; Bowers 1984; Goodwin 1993; Joyce and Paykel 1989; Sotsky et al 1991). By none of these means was it possible to predict which patient will respond to treatment and which patient will remain refractory.

The contention that secondary amine antidepressants, like desipramine and reboxetine are more suitable for the treatment of depression with motor retardation (Kielholz 1968), than tertiary amines, e.g., imipramine and amitriptyline, was not borne out by evidence. Hypotheses that depression with low concentrations of urinary 3-methoxy-4-phenylglycol (MHPG), the final metabolic end product of NE, respond to selective NE reuptake blockers, whereas depression with low cerebrospinal fluid (CSF) concentrations of 5-hydroxy-indole-acetic acid (5HIAA), the final metabolic end product of 5-HT, respond to selective 5-HT reuptake blockers, could not be substantiated in clinical experiments (Potter et al 1985; Schatzberg 1998). In the mid-1980s it was shown that desipramine, a selective NE re-uptake inhibitor, and zimelidine, a selective 5-HT reuptake inhibitor, both decreased MHPG) and 5-HIAA concentrations in the CSF (Potter et al 1985). To date, no consistent relationship could be revealed between NE and 5-HT blocking potencies of antidepressants and therapeutic effects (Ban 1999).

The only consistent predictor for responsiveness to a particular drug is based on the clinical impression that in different episodes the same patient tends to respond to the same drug (Pare and Mack 1971).

Development of the methodology employed in clinical investigations in the second half of the 20th century was triggered by the difficulties encountered in the demonstration of therapeutic efficacy of imipramine and the notion that the difficulties encountered were due to the lack of sensitive instruments for the detection of antidepressant effects. By overlooking the relationship between the heterogeneity of the depressive population and difficulties for demonstrating efficacy,

concentrated efforts were directed for developing instruments which are sufficiently sensitive for changes in the severity of symptoms to detect antidepressant effects. This was in-keeping with the interest of the pharmaceutical industry, which had several imipramine-like drugs ready in their pipelines for clinical development. It was also in line with the thinking of practicing psychiatrists, at the time, who were looking for clinically effective and hopefully even with more effective antidepressants than imipramine. The success of developing a methodology with reliable clinical diagnostic end-points and rating scales which were sensitive for the detection of changes to demonstrate therapeutic efficacy was counterproductive for identifying the treatment responsive forms of illness to the different antidepressants.

At the time the first generation of antidepressant drugs were introduced, psychiatry was struggling to reconcile widely different orientations, from social and psychodynamic to biological. The primary purpose of the DSM-III of the American Psychiatric Association (1980), the first widely accepted consensus based classification, was the creation of a common language and not the provision of diagnostic end-points for clinical investigations with psychotropic drugs. To accommodate the different orientations in psychiatry, the diagnostic categories of the DSM-III are broad and by accommodating the different forms of disease, in a limited number of diagnoses, the various diagnostic categories are heterogeneous and their predictive validity are low. The problems of the DSM-III and its successors, i.e., DSM-III-R and DSM-IV, are compounded by their success (American Psychiatric Association 1987, 1994). While providing reliable clinical end-points for clinical drug development, i.e., demonstration of therapeutic efficacy, and for the communication of approved indications of antidepressants, consensus-based classifications have become one of the major obstacles to the identification of the treatment responsive forms of illness to antidepressants.

Another major obstacle is the sensitized scales used in the demonstration of therapeutic efficacy of antidepressants. Rating scales can be sensitized by the omission of psychopathological symptoms relevant to disease, which are not influenced by treatment, or by retaining only those items (variables) of a scale which show the largest changes. Montgomery and Asberg's Depression Scale (Montgomery and Asberg 1979) was derived by such compromises from the Comprehensive Psychiatric Rating Scale developed in Sweden (Asberg et al 1978; Perris 1986; Sartorius and Ban 1986). While the use of sensitive scales helps to demonstrate therapeutic efficacy in the shortest

possible time in the smallest number of patients, the omission of psychopathological symptoms (variables) relevant to different forms of disease, has precluded the possibility of finding any relevant information for the identification of the treatment responsive forms of illness (subgroups of patients) in the vast data bases by meta-analyses.

COMPOSITE DIAGNOSTIC EVALUATION OF DEPRESSIVE DISORDERS

To break the impasse in improving the response rate to antidepressants, there is a need for a shift in emphasis in clinical research from the demonstration of therapeutic efficacy to the identification of treatment responsive form(s) of illness (Ban 1987). For studying the differential effect of the same drug in different forms of illness consensus-based diagnostic end-points and sensitized rating scales do not suffice. They need to be supplemented/replaced with composite diagnostic evaluations or comprehensive psychopathologic check lists, constructed with consideration of the historical development of diagnostic concepts (Ban 1989).

THE CODE SYSTEM

The Composite Diagnostic Evaluation or CODE System is a set of diagnostic instruments which by specially devised algorithms can assign a diagnosis from several diagnostic systems simultaneously to the same patient. Each instrument (CODE) consists of an integrated criteria list, i.e., a set of symptoms ("codes") which, on the basis of standardized data collection, yield diagnoses in all the component diagnostic systems; a semi-structured interview, suitable for the elicitation of all the symptoms in terms of "present," or "absent;" and diagnostic decision trees, which organize symptoms into distinct psychiatric illnesses (Ban 2001). The CODE-System differs from other poly-diagnostic evaluations by its capability to provide readily accessible information relevant to the diagnostic process from the lowest to the highest level of decision making (Ban 1992).

Development of the CODE System began in the late 1980s with CODE-DD, the composite diagnostic evaluation of unipolar depression (Ban 1989). It continued with the development of CODE-HD, the composite diagnostic evaluation of hyperthymic disorders (Gaszner and Ban 1998),

and culminated in the development of CODE-SD, the composite diagnostic evaluation of schizophrenic disorders (Ban 1994).

CODE-DD

The prototype of all CODEs is CODE-DD. It consists of a 90 item Rating Scale for Depressive Diagnoses (RSDD) with a 40 items subscale, the Rating Scale for the Assessment of Severity of Depressive Disorders (RSASDD) and a Glossary of Variables in Depressive Disorders(VDD); a Semi-Structured Interview for Depressive Disorders (SSIDD); and decision trees which, as shown in table 15, provide diagnoses in 25 different classifications of depression.

TABLE 15

1. KRAEPELIN 1891
2. SCHNEIDER 1920
3. LEONHARD 1957
4. LEWIS 1934
5. HAMILTON & WHITE 1959
6. KILOH & GARSIDE 1963
7. POLLITT 1965
8. OVERALL ET AL. 1966
9. MENDELS & COCHRANE 1968
10. PILOWSKY ET AL. 1969
11. PAYKEL 1971
12. ROBINS & GUZE 1972
13. KIELHOLZ 1972
14. FEIGHNER & AL 1972
15. FOULDS 1973
16. KLEIN 1974

17. WING ET AL 1974
18. RASKIN & CROOK 1976
19. SPITZER & AL 1978
20. WINOKUR 1979
21. TAYLOR & AL 1981
22. BERNER & AL 1983
23. DSM-III 1967
24. ICD-9 1988
25. COMPOSITE DIAGNOSTIC CLASSIFICATION (BAN) 1989

The 25 diagnostic classifications included in CODE-DD

Administration of CODE-DD is completed during a 30 to 40 minutes interview which can be carried out with or without computer prompting. The computer program developed in the 1980s was in the Fortran programming language for the MS-DOS program (Ban et al 1993).

In spite of concerns that inter-rater agreement in such a complex system as CODE-DD will be low, in the first reliability study (carried out with the participating investigators of a multinational clinical trial) there was a median item agreement of 87.8% with a higher than 80% agreement for 74 of the 90 variables (Ban 1991, 1992). In the second reliability study, item agreement increased to 100%. There was also a 100% agreement in the third study, with a 100% agreement for the 25 diagnostic systems, and with an overall kappa coefficient of 1.00 (Ban et al 1993).

Analyses of CODE-DD data from the first study revealed that the DSM-III-R diagnosis of major depression is a broad diagnostic category (Ban 1992). As shown in table 16, from the 230 patients included in the study with the clinical diagnosis of major depression, 13.5% or more did not fit any of the depressive diagnoses in six classifications. As many as 77 patients, i.e., 35.5% of the total population with the clinical diagnosis of major depression in the DSM-III-R, did not meet the Vienna Research Criteria of depression (Berner et al. 1983).

TABLE 16

CLASSIFICATIONS	PATIENTS	
	N	%
Vienna Research Criteria	77	33.5
Kraepelin	54	23.5
Leonhard	41	17.8
Hamilton & White	36	15.7
Research Diagnostic Criteria	31	13.5
Overall et al	31	13.5

Number and % of patients from the total sample of 230 patients with the diagnosis of major depression who could not be classified as depressed in 6 of the 25 classifications of CODE-DD

The finding that the DSM-III-R diagnosis of major depression is a broad diagnostic category received further substantiation in the second study in which analyses of CODE-DD data revealed that, if depressive illness is characterized by unmotivated depressed mood, depressive evaluations, and lack of reactive mood changes, from the 322 patients included in the study only 119 patients (37%) fulfilled definite (all three variables present) criteria of depression with an additional 91 patients (28.2%) fulfilling probable (two of the three variables present) and 61 patients (19%) fulfilling possible (one of the three variables present) criteria.

Further analyses of data from the first and second studies indicated the Kraepelin's depressive states (KDS) and Schneider's vital depression (SVD) were nosologically distinct categories. In both studies, the overlap between patients who fulfilled definite criteria of KDS, characterized by the presence of the triad of depressed mood, motor retardation and thought retardation, and definite criteria of SVD, characterized by the triad of unmotivated depressed mood, corporization and feeling of loss of vitality, were less than expected by chance. If the nosologic distinctiveness would translate into pharmacological distinctiveness in terms of responsiveness to treatment, KDS and/or SVD would be suitable forms of depressive illness for

neuropsychopharmacological and molecular genetic research.

GENETICS, NEUROPSYCHOPHARMACOLOGY AND CODE-DD

Since all the primary targets of antidepressants are molecular structures involved in neuronal transmission, e.g., G-protein coupled receptors, nuclear (hormonal) receptors, enzymes, and all these structures are encoded by genes which are identified, any sub-population of depression which corresponds with an antidepressant treatment responsive population is suitable for the generation of genetic hypotheses using the candidate gene approach. Thus, if the antidepressanttreatment responsive populations could be identified neuropsychopharmacology by linking the effect of psychotropic drugs on mental illness with their action on brain structures, this would provide an adequate methodology for bridging the gap between the 15,000 to 17,000 genes in the human brain --which determine the structure and function of simple molecules (usually proteins in cells) and the cellular response-- and psychiatric diagnoses (Ban 2002; Faraone, Tsuang and Tsuang 1999).

Development of receptor binding assays during the 1970s and identification of receptor subtypes during the 1980s led to the delineation of the receptor profile of antidepressants. The new genetic technology allows for tailoring antidepressants to receptor affinities. By using cell lines transfected with cloned receptors for finding chemicals which fit specific receptors, according to Steven Paul (1996), a Vice President of Eli Lilly, an International Pharmaceutical Company, the new "computational structural biology" would allow the designing of antidepressants with receptor profiles which could fit diseases like keys their locks.

If the current capability of neuropharmacological research would be complemented with clinical psychopharmacological research focused on the identification of treatment-responsive forms of depressive illness and on the differential effects of new antidepressant drugs, it could open up a new perspective in the treatment of the different forms of “depression” covered by the diagnostic label of “major depression”. In the new perspective each different form of depression would get its own "magic bullet" (Carr 1998; Lerer and Macciardi 2002).

CONCLUSIONS

1. In spite of the steadily growing use of antidepressants, depression has become the fifth leading cause of disability by the end of the 20th century; and if current trends continue, it will become by 2020 the second (to coronary artery disease) leading cause of disability in the world.
2. The finding that only 1 of 3 depressed patients responds to the pharmacological action of the antidepressant drug first prescribed, indicates that depressive illness is pharmacologically heterogeneous and depression-induced disability can only be reduced significantly by the identification of the treatment responsive subpopulation to the different antidepressant drugs.
4. Neuropsychopharmacology would provide an adequate methodology for bridging the gap between depressive diagnoses and the genes if the treatment responsive populations to antidepressants could be identified.

REFERENCES

Adams F. Genuine Works of Hippocrates. Translated from the Greek. 2 volumes. New York: William Wood & Co; 1929.

American Psychiatric Association. Diagnostic and Statistical Manula of Mental Disorders (DSM-II). Washington: American Psychiatric Association; 1968.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Diorders. Third Edition (DSM-III). Washington: American Psychiatric Association; 1980.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Third-Revised (DSM-III-R). Washington: American Psychiatric Association; 1987.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth

Edition (DSM-IV). Washington: American Psychiatric Association; 1994.

American Psychiatric Associaion. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition. Text Revision (DSM-IVTM). Ninth Printing. Washington: American Psychiatric Association; 1999.

Asberg M, Perris C, Schalling D, Sedvall G. The CPRS-Development and application of a psychiatric rating scale. Acta Psychiatr Scand 1978; (suppl 271).

Aurelianus C. On Acute Diseases and on Chronic Diseases. Translated by IE Drabkin. Chicago: University of Chicago Press; 1950.

Ban TA. Psychopharmacology. Baltimore: Williams & Wilkins; 1969.

Ban TA. Depression and the Tricyclic Antidepressants. Montreal: Ronalds Federated; 1974.

Ban TA. Psychopharmacology of Depression. Basel: Karger; 1981.

Ban TA. Prolegomenon to the clinical prerequisite: Psychopharmacology and the classification of mental disorders, Prog. Neuro-Psychopharmacol. & Biol. Psychiat 1987; 11: 527-80.

Ban TA. Composite Diagnostic Evaluation of Depressive Disorders. CODE-DD. Brentwood: JM Productions; 1989.

Ban TA. The CODE system in psychiatric research. Psychopharmacologia 1991; 4: 41-49.

Ban TA. Composite diagnostic evaluation: Methodology and applications. In: F Ferrero, AE Haynal, N Sartorius (eds,) Schizophrenia and Affective Psychoses. Nosology in contemporary Psychiatry. Rome: John Libbey; 1992, pp. 41-49.

Ban TA. Composite Diagnostic Evaluation of Schizophrenic Disorders. CODE-SD. Mimeographed: Unpublished; 1994...

Ban TA. Selective drugs versus heterogenous diagnoses towards a new methodology in psychopharmacologic research. Psiqiatr Biol 1999; 7: 177-189

Ban TA. From DSM-III to DSM-IV: progress or standstill. In E Franzek, GS Ungvari, E Ruther, H Beckmann (eds.) Progress in Differentiated Psychopathology. Wurzburg: International Wernicke-Kleist-Leonhard Society; 2000, pp. 1-11.

Ban TA. The CODE system in psychiatry. Neuropsychophar macologia Hungarica 2001; 3: 6-10

Ban TA. Pharmacotherapy of depression: A historical analysis. Journal of Neural Transmisson 2001; 108: 707-716.

Ban TA. Genes, psychopharmacology and psychiatric nosology. In: Lerer B, (ed) Pharmacogenetics and Psychotropic Drugs. Cambridge: Cambridge University Press; 2002, pp. 36-51.

Ban TA, Fjetland O, Kutcher M, Morey LC. CODE-DD: Development of a diagnostic scale for depressive disorders. In: I Hindmarch, PD Steiner (eds.) Human Psychopharmacology. Measures and Methods. Chichester: John Wiley & Sons; 1993, pp. 73-85

Ban TA, Schwartz L. Systematic studies with levomepromazine. J Neuropsychiat 1963; 5: 112-117.

Beck AT. Depression. London: Staples; 1967.

Berner P, Gabriel E, Katschnig H, Kieffer W, Koehler K, Lenz G, Simhandl Ch. Diagnostic Criteria for Schizophrenic and Affecticive Psychoses. Washington: World Psychiatric Association; 1983.

Besendorf H, Pletscher A. Beeinflussung zentraler Wirkungen von Reserpin und 5-hydroxytryptamin durch Isonicotinhydrazide. Helv Physiol Acta 1956; 14: 383-390.

Billings EG. A Handbook of Elemenraty Psychobiology and Psychiatry. New York: The Macmillan Company; 1939.

Blackwell B. Hypertensive crisis to MAOI. Lancet 1963; ii: 849-851.

Blaschko H, Richter D, Scholassman H. The inactivation of adrenaline. J Physiol 1937; 90: 1-9.

Blazer DG, Kessler RC, McGonagle KA, Swartz MS. The prevalence and distribution of major depression in national cmmunity samples: the National Comorbidity Survey. Am J Psychiatry 1994; 151: 979-986.

Blumenthal MD, Dielman TE. Depressive symptomatology and role function in a general population. Arch Gen Psychiatry 1975; 32: 985-991

Bonhoeffer K. Die Symptomatischen Psychosen. Leipzig: Deuticke; 1910.

Bowers MB. Family history of CSF homovanillic acid pattern during neuroleptic treatment. Amer J Psychiatry 1984; 141: 296-298.

Bright T. A Treatise of Melancholia. London: Thomas Vautrollier; 1586.

Brodie BB, Bickel MH, Sulser F. Desmethylimipramine, a new type of antidepressant drug. Med Exp 1961; 5: 454-458.

Brown GW, Davidson S, Harris T, et al. Psychiatric disorders in London and North Vist. Soc Sci

Med 1977; 11: 367-377.

Brown GW, Harris T. Social Origins of Depression. A Study of Psychiatric Disorders in Woman. London: Tavistock; 1978.

Bruel O (1957) Behandlung der Depressionszustanden mit haematoporphyrin. Nencki Psychiat Neurol 1957; 133: 1-7.

Brunet F. Oevres Medicales D'Alexandre de Tralles. French translation with introduction and comments. 4 volumes. Paris: Geuthner; 1933.

Burton R. The Anatomy of Melancholy (1621). New York: Tudor; 1948.

Carlsson A. Neuropharmacology. In TA Ban, D Healy, E Shorter (eds.) The Rise of Psychopharmacology and the Story of CINP. Budapest: Animula; 1998, pp. 124-128.

Carr G. The pharmaceutical industry. The Economist, February 1998; 21: 3-18

Celsus AC. De Medicina. Translated by Walter George Spencer. 3 volumes. London: Heinemann; 1935.

Chiarugi V. Della Pazzia in Genere e in Specie con Una Centuria di Ozzervazioni. 3 volumes. Florence: Carlieri; 1793-1794.

Chisholm D. The economic consequences of depression. In: A Dawson, A Tylee (eds.) Depression: Social and Economic Timebomb. London: BMJ Books 2001, pp. 121-129

Cohen BM, Fairbank RE. Statistical contribution from the mental hygiene study of the eastern health district of Baltimore. Am J Psychiatry 1938; 94: 1153-1161.

Costa E, Garattini S, Valzelli L. Interactin between reserpine, chlorpromazine and imipramine. Experientia 1960; 15: 461-463.

Crane GE. Iproniazid (Marsalid) phosphate: a therapeutic agent for mental disorders. Psychiatr Res Reports 1957; 8: 142-154.

Cullen W. Synopsis Nosologiae Methodicae. Edinburgh: A. Kincaid & Creech; 1769.

Davies DI, Shepherd M. Reserpine in the treatment of anxious and depressed patients. Lancet 1955; II: 117-121.

Davis JM, Wang Z, Janicak PG. A quantitative analysis of clinical drug trials for the treatment of affective disorders. Psychopharmacol Bull 1993; 129: 175-81

Dawson A, Tylee A, eds. Depression: Social and Economic Timebomb. London: BMJ Books; 2001.

Delay J, Laine B, Buisson JF. Anxiety and depressive states treated with isonicotinyl hydrazide (isoniazid). Arch Neurol Psychiatry 1952; 70: 317-324.

Domenjoz R, Theobold W. Zur Pharmacologie des Tofranil. Arch Int Pharmcodyn 1959; 129: 450-489.

Duncan-Jones P, Henderson S. The successful use of a two-phase design in a population survey. Soc Psychiatry 1978; 12: 231-237.

Eaton JW, Weil RJ. Culture and Mental Disorders: A Comparative Study of the Hutterites and Other Populations. New York: Free Press; 1955.

Esquirol JED. De la lypémanie ou melancolie. Paris: Baillier; 1820.

Esquirol JED. Des maladies mentales. vol.2. Paris: Bailliere; 1838.

Faber K. Nosography in Modern Internal Medicine. New York: Hoeber; 1923.

Faraone SV, Tsuang MT, Tsuang DW. Genetics of Mental Disorders. New York: Guilford Press; 1999.

Feighner JP, Robins E, Guze SB, Woodruff JP, Winokur G, Munoz R. Diagnostic criteria for use in psychiatric research. Arch Gen Psychiatry 1972; 26: 57-63.

Foulds GA. The relationship between the depressive illnesses. Brit J Psychiatry 1973; 122: 531-533.

Foulds GA. The Hierarchical Nature of Personal Illness. Orlando: Academic; 1976.

Garrison FH. An Introduction to the History of Medicine. Fourth Edition. Philadelphia: W.B. Saunders Company; 1929.

Garrison FH. An Introduction to the History of Medicine. Fifth Edition. Philadelphia: W.B. Saunders Company; 1980.

Gaszner P, Ban TA. CODE-HD Composite Diagnostic Evaluation of Hyperthymic Disorders. Budapest: Animula; 1998.

Gill HS, Devane CC, Risch SC. Extrapyramisal symptoms associated with cyclic antidepressant treatment: a review and consolidating hypothesis. Journal of Clinical Psuchopharmacology 1997;

17: 377-389.

Gillis A, Salfield DG (1953) Treatment of depressive states with dinitrile succinate. J Ment Sci 1953; 99: 542-548.

Goodwin FK. Predictors of antidepressant response. Bulletin of the Menninger Clinic 1993; 57: 146-160.

Hamilton M, White JM. A rating scale for depression. J Neurol Neurosurg Psychiatry 1959; 23: 958-990.

Healy D. The Antidepressant Era. Cambridge: Harvard University Press; 1997.

Healy D. The Creation of Psychopharmacology. Cambridge: Harvard University Press; 2002.

Heinroth JCh. Lehrbuch der Storungen des Seelenlebens. Leipzig: Vogel; 1818.

Hoenig J. The early manifestations of depression: diagnostic hints. In FJ Ayd (ed.) Clinical Depressions: Diagnostic and Therapeutic Challanges. Baltimore: Ayd Medical Communications; 1980, pp. 1-21.

Hollister LE. The beginning of psychopharmacology. A Personal account. In: TA Ban, D Healy, E Shorter (eds.) The Rise of Psychopharmacology and the Story of CINP. Budapest: Animula; 1998, pp. 41-44.

Horwath E, Weissman MM. Epidemiology of depression and anxiety disorders. In MT Tsuang, M Tohen, GEP Zahner (eds) Textbook in Psychiatric Epidemiology. New York; Wiley-Liss; 1995,, pp. 317-344

House A. Against the motion. In A Dawson, A Tylee (eds.) Depression: Social and Economic Timebomb. London: BMJ Books; 2001, pp. 173-176.

Hunter R, Macalpine I. Description of the Retreat by Samuel Tuke. London: Dawson & Pall Mall; 1964.

Janowsky D. Thinking of neurotransmitters. Moods and psychoses in the 1960s and 1970s. In: Ban TA, Healy D, Shorter E (eds.) The Triumph of Psychopharmacology and the Story of CINP. Budapest: Animula; 2000, pp 275-9.

Janowsky D, El Yousef MK, Davis JM. Acetylcholine and depression. Psychosom Med 1974; 36: 248-57.

Joyce PR, Paykel ES. Predictors of drug response in depression. Archives of General Psychiatry 1989; 46: 89-99.

Kahlbaum KL. Die Gruppierung der psychischen Krankheiten . Entwurf einer historisch-kritischen Darstellung der bisherigen Einteilungen und Versuch zur Anbahnung einer empirisch-wissentschaftlichen Grundlage der Psychiatrie als klinischer Disziplin. Danzig: A.W. Kaufman; 1863.

Kaplan HI, Sadock BJ. Synopsis of Psychiatry. Behavioral Sciences Clinical Psychiatry. Fifth Edition. Baltimore: Williams & Wilkins; 1988.

Keller MB, Klein DF, Hirschfeld RM, et al. Results of the DSM-IV mood disorders field trial. Am J Psychiatry 1995; 152: 843-849.

Keller MB, McCullogh JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N

Engl J Med 2000; 342: 1462-1470

Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994; 12: 518-519.

Khan A, Khan S, Brown WA. Are placebo controls necessary to test new antidepressants and anxiolytics. International Journal of Neuropsychopharmacology 2002; 5: 193-7.

Kielholz P. Die Behandlung endogener Depressionen mit Psychopharmaka. Deutsche Chirurg med Wschr 1968; 93: 701-703.

Kielholz P. Diagnostic aspects in the treatment of depression. In: Kielholz P (ed.). Depressive Illness. Bern: Hans Hubert; 1972.

Kiloh LG, Garside RF. The independence of neurotic depression and endogenous depression. Brit J Psychiatry 1963; 109: 451-463.

Klein DF, Davis JM (1969) Diagnosis and Drug Treatment of Psychiatric Disorders. Baltimore: Williams & Wilkins

Klein DF. Endogenomorphic depression. Arch Gen Psychiatry 1974; 31: 447-454.

Klein SA. Book's claims about SSRIs unleashes angry backlash. Psychiatric News 2000; 35: 8-30.

Kleinman A, Cohen A. A global view of depression from an anthropological perspective. In A Dawson, A Tylee (2001) Depression: Social and Economic Timebomb. London: BMJ Books; 2001, pp. 11-15

Klerman GL, Cole JO. Clinical pharmacology of imipramine and related antidepressant compounds. Pharmacol Reviews 1965; 17: 101-141.

Knoll J. Deprenyl, the first catecholaminergic enhancer. In: TA Ban, D Healy, E Shorter (eds.) The Rise of Psychopharmacology and the Story of CINP. Budapest: Animula; 1998. pp. 91-94.

Kraepelin E.Compendium der Psychiatrie. Leipzig: Abel; 1883.

Kraepelin E (1887) Ein Kurzes Lehrbuch der Psychiatrie. 2 Aufl. Leipzig: Barth;1887.

Kraepelin E Ein Kurzes Lehrbuch. 3 Aufl. Leipzig: Barth; 1889.

Kraepelin E Ein Kurzes Lehrbuch der Psychiatrie. 4 Aufl. Leipzig: Barth; 1891.

Kraepelin E. Lehrbuch der Psychiatrie. 5 Aufl. Leipzig: Barth; 1896.

Kraepelin E. Lehrbuch der Psychiatrie. 6 Aufl. Leipzig: Barth; 1899.

Kraepelin E. Lehrbuch der Psychiatrie. 7 Aufl. Leipzig: Barth; 1904..

Kraepelin E. Lehrbuch der Psychiatrie. 8 Aufl. Leipzig: Barth; 1913.

Kuhn R. Ueber die Behandlung depressives Zustande mit einem iminodibenzylderivat (G22,355). Schweiz Med Wochenschrift 1957; 87: 1135-1140.

Kuhn R. Corrections of statements in the publication by David Healy on the history of the discovery of modern antidepressants. In: TA Ban, D Healy, E Shorter (eds.) From Psychopharmacologgy to Neuropsychopharmacology in the 1980s and the Story of CINP As Told in Autobiography. Budapest: Animula; 2002, pp. 301-308.

Langer SZ, Moret C, Raisman R, et al. High affinity 3H-imipramine binding in rat hypothalamus. Association with uptake of serotonin, but not of norepinephrine. Science 1980; 210: 1133-1135.

Leighton DC, Harding JS, Macklin DB, et al. Psychiatric findings of the Sterling County study. Am J Psychiatry 1963; 55: 1021-1026.

Lemkau PV, Tietze C, Cooper M. Mental hygiene problems in an urban district. II. The psychotics and the neurotics. Ment Hyg 1942; 26: 100-119.

Leonhard K. Aufteilung der endogenen Psychosen. Berlin: Akademie-Verlag; 1957.

Lerer B, Macciardi F. Pharmacogenetics of antidepressants and mood-stabilizing drugs: a review of candidate-gene studies and future research directions. International Journal of Neuropsycho-pharmacology 2002; 5: 255-275

Lewis A. Melanchoila: s clinical survey. Journal of Mental Science 1934; 60: 277-378.

Lewis WH. Iatrogenic psychotic depressive reaction in hypertensive patients. Am J Psychiatry 1971; 127: 1416-1417.

Lin T. A study of the incidence of mental disorders in Chinese and other cultures. 1953; 16: 313-336.

Loomers HP, Saunders JC, Kline NS . A clinical and pharmacodynamic evaluation of iproniazid as a psychic energizer. Psychiatri Res Reports 1957; 8: 129-141.

Mapother E. Discussion on manic-depressive psychosis. British Medical Journal 1926; 2; 872-876.

Mayer-Gross W, Slater E, Roth M. Clinical Psychiatry. Revised Second Edition. London: Cassell and Company Ltd; 1960.

Mendels J, Cochrane C. The nosology of depression: The endogenous-reactive concept. Am J Psychiatry 1968; 124 (supplement): 1-11

Menninger K, Mayman M, Pruyser P. The Vital Balance. The Life Process in Mental Health and Illness. New York: The Viking Press; 1968.

Meyer A. Objective psychology or psychobiology with subordination of the medically useless contrast of mental and physical. JAMA 1915; 45: 860-863.

Meyer A. Collected Papers. 2 volumes. Baltimore: Johns Hopkins Press; 1952.

Michalak EE, Lam RW. Breaking the myths: new treatment approaches for chronic depression. Can J Psychiatry 2002; 47: 635-643.

Moebius JP. Abriss der Lehre von den Nervenkrankheiten. Leipzig: Barth; 1893.

Montgomery S, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134: 382-389.

Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease study. Lancet 1997; 349: 1498-1504.

Nyirö Gy. Pszichiatria. Budapest: Medicina; 1962.

Overall JE, Hollister LE, Johnson M, Pennington V. Nosology of depression and differential response to drugs. JAMA 1966; 195: 946-948.

Pare CMB, Mack JW (1971) Differentiation of two specific types of depression by the response to antidepressant drugs. Journal of Medical Genetics 1971; 8: 306-309

Patten SB. Progress against major depression in Canada. Can J Psychiatry 2002; 47: 775-780

Paul SM. Lilly: Advancing CNS research into the twentyfirst century. J Clin Psychiatry 1996; 57: 325-326.

Paul SM, Rehavi M, Skolnick P, Goodwin FK. Demonstration of high affinity binding sites for [3-H] imipramine in human platelets. Life Sci 1980; 26: 953-959.

Paykel ES. Classification of depressed patients: A cluster analysis derived grouping. Brit J Psychiatry 1971; 118: 275-288.

Pearson P (2002) I need a pill right now. National Post, Wednesday, September 18, 2002.

Perris C Rating depression with a subsacle of the CPRS. In N Sartorius, TA Ban (eds.) Assessment of Depression. Berlin: Springer; 1986, pp. 99-107.

Pilowsky I, Levine S, Boulton DM. The classification of depression by numerical taxonomy. Brit J Psychiatry 1969; 115: 937-945.

Pinel P. Nosographie philosophique, ou methode de l'analyse appliquee a la medecine. Paris: Richard, Caille et Ravier; 1798.

Pinel P. Traite medico-philosophique sur l'alienation mentale, ou la manie. Paris: Richard, Caille et Ravier; 1801.

Politt JD. Suggestions for a physiological classification of depression. Br J Psychiatry 1965; 111: 489-495.

Potter MZ, Scheinin M, Golden RN, et al. Selective antidepressaants and cerebrospinal fluid. Arch Gen Psychiatry 1985; 42: 1171-1177

Pugh CE, Quastel JH. Oxidase of aliphatic amines by brain and other tissues. Biochem J 1937; 31: 286-291.

Raskin A, Crook T. The endogenous-neurotic distribution and a predictor of response to antidepressant drugs. Psychol Med 1976; 6: 59-70.

Ravindran AV, Anisman H, Merali Z, et al. Treatment of primary dysthymia with group cognitive therapy and pharmacotherapy: clinical symptoms and functional impairments. Am J Psychiatry 1999; 156: 1608-1617.

Rees WL. Treatment of depression by drugs and other means. Nature 1960; 186: 114-120.

Reid T (1764) An Inquiry into the Human Mind, on the Principles of Common Sense. Glasgow; 1764.

Robins E, Guze SB.Classification of affective disorders: the primary-secondary, endogenous-reactive and the neurotic-psychotic concepts. In TA Williams, MM Katz, JA Shield (eds) Recent Advances in Psychobiology of the Depressive Illnesses. Washington: US Government Printing Office; 1972.

Salzer HM, Lurie ML. Anxiety and depressive states treated with isonicotinyl hydrazide (isoniazid). Arch Neurol Psychiatry 1997; 70: 317-324.

Sargant W. Drugs in the treatment of depression. Br Med J 1961; I: 225-227.

Sartorius N, Ban TA eds. Assessment of Depression. Berlin: Springer; 1986.

Sauvages de la Croix, BF. Nosologia Methodica Sistems Morborum Classes, Genera et Species, Juxta Sydenhami Mentem et Botanicorum Ordinem. 5 volumes. Amsterdam: Frat de Tournes; 1768.

Schatzberg AF. Noradrenergic versus serotonergic antidepressants. Predictors of treatment response. J Clin Psychiatry 1998; 59 (supplement 14): 15-18.

Schneider K. Die Schichtung des emotionalen Lebens und der Aufbau der Depressions zustande. Z ges Neurol Psychiat 1920; 59: 281-285.

Schneider K. Psychopathic Personalities. Translated by MW Hamilton. London: Cassell; 1958.

Selbach H Ueber die vegatative Dynamik in der sychiatriscen Pharmakotherapie. Dtsch Med Wochenschr 1959; 12: 511-7.

Selikoff IJ, Robitzek EH, Orenstein GG. Treatment of pulmonary tuberculosis with hydrazine derivatives of isonicotinic acid. JAMA 1952; 150: 973-980.

Shopsin B, Friedman E, Gershon S. Parachlorophenylalanine reversal of tranylcypromine effects in depressed patients. Arch Gen Psychiatry 1976; 33: 811-819.

Shopsin B, Gershon S, Goldstein M, et al. Use of synthetic inhibitors in defining a role for biogenic amines during imipramine treatment of depressed patients. Psychopharmacol Commun 1975; 1: 239-249.

Sotsky SM, Glass DR, Shea MT, et al. Patient predictors of response to psychotherapy and pharmacotherapy: findings in the NIMH Treatment of Depression Collaborative Research Program. American Journal of Psychiatry 1991; 148: 997-1008.

Silverman C. Epidemiology of depression. Am J Psychol 1968; 124: 883-891.

Spitzer R, Endicott J, Robins E. Research Diagnostic Criteria (RDC) for Selected Group of Functional Disorders. New York: New York State Psychiatric Institute; 1978.

Sulser F, Watts J, Brodie BB. On the mechanism of antideperessant action of imipramine-like drugs. Ann NY Acad Sci 1962; 96: 273-286.

Taylor MA, Redfield J, Abrams R. Neuropsychological dysfunction in schizophrenia and affective disease. Biol Psychiatry 1981; 16: 467-469.

Trindade E, Menon D, Topfer LA, Coloma C. Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants. : a meta-analysis. CMAJ 1998; 159: 1245-52.

Tuke S. Description of the Retreat. York: Printed for W. Alexander; 1813.

Vaisanen E. Psychiatric disorders in Finland. Acta Psychiatr Scand Suppl 1975; 263: 22-33.

Vetulani J, Stawarz R, Pingell J, Sulser F. A possible common mechanism of antidepressant drugs. NS Arch Pharmacol 1975; 243: 109-111.

Walker L Sertralinre-induced akathisia and dystonia misinterpreted as a panic attack. Psychiatric Services 2002; 53: 1477-1478.

Weissman MM, Myers JK. Affective disorders in a United States urban community: the use of

research diagnostic criteria in an epidemiological survey. Arch Gen Psychiatry 1978; 35: 1304-1311.

Whitaker J. Reversing Heart Disease. New York: Warner Books Inc; 2002.

Wimmer A. Psykogene Sindssygdomsformer. In St. Hans Hospital 1816-1916. Copenhagen: Jubilee Publication; 1916, pp. 85-216.

Wing JK Cooper JE, Sartorius N. Classification of Psychiatric Symptoms. Cambridge: Cambridge University Press; 1974.

Winokur G. Unipolar depression: is it divisible into autonomous subtypes. Arch Gen Psychiatry 1979; 36: 47-52

World Health Organization. International Classification of Diseases (ICD-8). Geneva: World Health Organisation; 1969.

World Health Organization. ICD-10, 1987 Draft of Chapter V (Categories F) Mental, Behavioural and Developmental Disorders: Clinical Descriptions and Diagnosis Guidelines. Geneva: World Health Organization; 1988.

World Health Organisation. The ICD-10 Classification of Mental and Behavioural Disorders. Geneva: World Health Organization; 1993.

World Health Organization. World Health Report 1999: Making a Difference. Geneva: World Health Organization; 1999.

Youdim MBH. Some observations upon a new inhibitor of monoamine oxidase in brain tissue. Biochem Pharmacol 1967; 17: 1285-1297.

Zeller EA, Barsky JR, Fouts W , et al. Influence of isonicotinic acid hydrazide (INH) and l-isonicotinyl-2 isoproyl hydrazide (IIH) on bacterial and mammalian enzymes. Experientia 1953; 8: 349-350.

Thomas A. Ban
March 6, 2014