

## **Thomas A. Ban: From Melancholia to Depression**

### **A History of Diagnosis and Treatment**

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This collated document includes Thomas A. Ban's essay posted in e-books on March 6, 2014, and the exchange that followed the posting between Hector Warnes and Ban. The essay was originally written for a presentation in 2002 and was posted unchanged.

This document is now open to all INHN Members for final comment.

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### **A History of Diagnosis and Treatment**

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## 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 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 seven to 10 times greater than the highest figures before the introduction of antidepressant drugs (Silverman, 1968).

**TABLE 1**

<b>AUTHOR</b>	<b>YEAR</b>	<b>%</b>
Cohen and Fairbank	1938	0.8
Lemkau et al	1941	0.9
Lin	1952	0.4
Eaton and Weil	1955	0.9

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Leighton et al	1963	7.5
Blumenthal and Dielman	1975	13
Vaisanen	1975	7.5
Brown et al	1977	8.0 - 10.0
Brown and Harris	1978	15.0 - 17.0
Duncan-Jones and Henderson	1978	11
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. (Silverman, 1968; 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-IVTR), 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**

<b>DIAGNOSES</b>	<b>LIFE TIME RISK</b>	<b>POINT PREVALENCE</b>
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%	7.5

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 20<sup>th</sup> 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 CLINICAL FEATURES	DEPTH OF DEPRESSION			
	None	Mild	Moderate	Severe
Stooped posture	6	32	70	98
Diurnal variation	16	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 and 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

under treated 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 one of three 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, BCE). 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 centuries 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, AD) 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 7<sup>th</sup> century, by Jean Fernel (1497-1558) in the 16<sup>th</sup> and, ultimately, by Robert Burton (1621) in the 17<sup>th</sup>. 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 17<sup>th</sup> 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*. Stimulated 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 of 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**

<b>Class of Illness</b>	
<i>Pinel</i>	<i>Esquirol</i>
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 19<sup>th</sup> 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 one 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 involitional 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) "lypomania"] 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
Bonhoeffer	Moebius	Wimmer
1910	1900	1916

SCHNEIDER (1920, 1958)

Depressive	VITAL	REACTIVE
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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-Kraepelinian 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 (ICD) 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 one of four diagnoses: involuntional 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**

<i>ICD-10</i>	<i>DSM-IV</i>
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 two of the three typical symptoms (in capitals) and two or more of the other seven symptoms must be present; to qualify for major depression in DSM-IV, five or more of the nine symptoms must be present including at least one of the two typical symptoms

**TABLE 11**

<i>ICD-10</i>	<i>DSM-IV</i>
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 19<sup>th</sup> 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 to date with 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 somniferum*, 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 16<sup>th</sup> 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-18<sup>th</sup> 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 19<sup>th</sup> century by Kraepelin (1891). An opium cure was a three week 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 (Bruehl, 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 in the 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 involuntional 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 iproniazid, 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 MAOIs steadily grew in spite of the long time (approximately eight years) required to demonstrate the therapeutic effectiveness of imipramine, the prototype MAOI, by Klerman and Cole (1965). Their report was based on a pooled analysis of data from 23 studies with a total of 1,009 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 two of three patients included in those studies had a favorable response, but only in one of the two 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 Theobald, 1959), without offering any clues as to 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 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  $\beta$ -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 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<sub>2A</sub> receptors and the inhibitory effect of serotonergic input to the dopaminergic pathways in the basal ganglia (Gill, Devane and Risch, 1997; Walker, 2002), a series of new antidepressants emerged in the 1990s. One of the first was venlafaxine, a nonselective but prevalently 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<sub>2</sub> and has weak inhibiting effect on 5-HT reuptake, and mirtazepine, a noradrenaline and serotonin selective agent (NaSSE), pharmacologically related to mianserin and trimipramine, which has no effect on 5HT reuptake (Ban, 1999).

#### ANTIDEPRESSANTS IN CLINICAL USE (Canada)

At present, in the early years of the 21<sup>st</sup> century, as shown in Table 10, there are 22

antidepressants available for clinical use in Canada: six nonselective re-uptake inhibitors including four prevalingly NE re-uptake blockers (SNRI-NA), and two prevalingly 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**

<i>PHARMACOLOGICAL CLASS</i>	<i>DRUGS</i>
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 Tranlycypromine
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 probability from placebo in 52 clinical trials with eight 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 the meta-analyses of Davis et al. (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 two of three 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**

DRUGSRESPONSE 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**  
EVENT RATE

SIDE EFFECTS	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 20<sup>th</sup> 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-item 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 ET AL. 1972

15. FOULDS 1973
16. KLEIN 1974
17. WING ET AL. 1974
18. RASKIN & CROOK 1976
19. SPITZER ET AL. 1978
20. WINOKUR 1979
21. TAYLOR ET AL. 1981
22. BERNER ET 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 minute 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 six 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 antidepressant treatment responsive populations could be identified neuropsychopharmacology, by linking the effect of psychotropic drugs on mental illness with their action on brain structures, 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 20<sup>th</sup> 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 one of three 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.



3. 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.

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March 6, 2014

### **Hector Warnes' Comment**

I was in awe reading your e-Book. I could not agree more that there is a

“pharmacological heterogeneity of depressive illness” and that “it is not possible to predict which patient will respond to treatment and which patient will remain refractory.” I also appreciate very much your CODE or Composite Diagnostic Evaluation, about which I would like to learn more. I recall that Jules Angst studied families of depressed patients who responded to the same drug as did other members of the family who also had affective disorders, but not to others (pharmacogenetics), which you seem to support by citing Steven Paul’s computational structural biology as an important marker.

One problem that has blurred boundaries proposed by Kraepelin is quantifying the symptomatology and the intensity of depression, which is addressed by Pierre Pichot (see P. Kielholz, editor: *Depressive Illness*. Hans Huber Publishers, Switzerland, 1972). Pichot stated that we can divide up the patients on the basis of symptomatology and aetiology using either factorial analysis or typological analysis. Further, we can measure the changes in symptomatology using a global measurement of severity and finally, we can search for prognostic indicators based on the response to treatment. I have followed in my clinical praxis the nosology proposed by Paul Kielholz of somatogenic, endogenous and more socio-psychogenic depression, including neurotic depression, chronic characteropathy and reactive depression. In this classification, exhaustion (Erschöpfung) depression is compatible with the chronic fatigue syndrome and with the stress theories of Selye. In the same book edited by Kielholz, the chapter by Juan J. López Ibor on masked depression and depressive equivalents brings together psychosomatic pathology with clinical psychiatry and the neurosciences. He writes: “I put forward the thesis that certain forms of anxiety neurosis and so-called psychosomatic disease were superimposed on a phasic alteration in the endothymic background of the patient’s personality,” which has been accepted as of late by many studies of risk factors in most illnesses, particularly, cardiovascular ones. Masked depression is equivalent to larviert depression and latent depression. Already, Griesinger described a frontal headache as a “frontal dysthymia.”

López Ibor isolated a meralgia paresthetica, thymopathic vertigo, cardiac arrhythmias and nuchal pain and even Groen’s “syndrome shift” in psychosomatic disorders as compatible with depressive equivalents. HBM Murphy noted in cross-cultural studies that African patients are more likely to have somatizations while western patients are more likely to suffer from guilt and self-laceration (Murphy HBM, Wittkower ED and Chance NA, *Cross cultural inquiry into the symptomatology of depression*. *International Journal of Psychiatry* 1967; 3: 6-22).

A masterful chapter in the *Comprehensive Textbook of Psychiatry* (eds. Harold Kaplan

and Benjamin Sadock, William and Wilkins, Baltimore, 1985 vol. I) was published by Heinz E. Lehmann. In this monumental treatise, he set the criteria for a classification based on the outcome, the periodicity (chronopathology), the signs of endogenous (particularly severe anhedonia, loss of libido, retardation, early awakening and diurnal fluctuation) versus reactive depression, the symptoms (retarded or anxious depression), the biological markers and the treatment response. Lehmann includes the "vital depression" proposed by Kurt Schneider in 1920, which was associated with an endogenous depression and masked depression, in which dysphoria is overshadowed or masked by obvious somatic symptoms such as pain proneness, alcoholism, somatizations and finally the "underground" depressions or untergrund-depressionen, which are prone to addictions (suchtgefährdet). It was a mind-opening chapter because Lehmann covers the historical, descriptive, phenomenological, representational and even cartographical aspects.

I noticed that you did not include in your E-Book the names of Kretschmer, Freud and Akiskal. The first one, regarding pyknic constitution or body build (Körperbau) and cyclothymic temperament (Körperbau u. Charakter. Berlin-Göttingen-Heidelberg: Springer 1955). In 85 cases of manic-depressive illness, Kretschmer found that 68.2% were "pyknic" body build.

Freud distinguished neurasthenia or actual neurosis (an entity introduced by G.M Beard in 1869), which in my mind is akin to neurovegetative dystonia and consists in fatigability, aches, pains, paresthesias, insomnia, pathological bodily sensations, etc. from anxiety neurosis; and he even wrote about a neurasthenic melancholia, see vol. III, Freud's paper: "On the grounds for detaching a particular syndrome from neurasthenia under the description anxiety neurosis" (The Standard Edition-London-the Hogarth Press, 1973). Angstneurose was a diagnosis first used by Freud. I have treated a few patients with classical neurasthenia, a diagnosis that still prevails in China.

Freud also distinguished mourning from melancholia (see Trauer und Melancholie-The Standard Edition vol. XIV) and E. Lindemann (Symptomatology and management of acute grief. American J. of Psychiatry 1944; 101: 141-8) went further in studying the cases of pathological grief.

Finally, H.S. Akiskal and O. Pinto (The soft bipolar spectrum: footnotes to Kraepelin on the interface of hypomania, temperament and depression. In: A. Marneros and J. Angst, Eds. Bipolar Disorder- Manic-Depressive Insanity. Dordrecht: Kluwer Academic Publishers; 2000, pp. 37-62), studied the so-called soft spectrum of bipolarities. He included an erratic personality

and a cyclothymic personality within about 12 subtypes. In another publication, *Psychiatric Developments* (1983; 2: 123-160), he refined the identification of subtypes based on categories, dimensions and biological markers (DST, REM latency, Test of TRH-TSH, Test of urinary excretion of MHPG, catechol-O-methyl-transferase, etc.).

This attempt of sorting out more and more subtypes to the point that there are even sub-clinical types reminds me of the complicated nosology of Wernicke-Kleist-Leonhard.

In my own clinical work, still there are many patients who cannot be fitted in any diagnostic category and one has to wait sometimes for 10 years to be able to understand their diagnostic formulation. A case in mind is an alcoholic patient who was admitted with delirium tremens, later developed a chronic delusional psychosis treated with depot neuroleptics and finally, after 20 years, he became hypomanic and I treated him with aripiprazole and lamotrigine with excellent result. The delusional psychosis just did not enter into the picture. Another case of a woman with chronic dysthymia, which started at puberty and at the age of 40, ended up in a major depression. Kraepelin wrote about a woman with melancholia who did not react to the death of her husband, but she did years later to the death of her dog. It is not easy to be as emphatic as Germán Berrios from Cambridge regarding reactive or minor depressions versus endogenous or major and primary versus secondary depression. He clarified the area of neurotic depression in a masterful lecture in Buenos Aires. I recommend his work bearing on the hermeneutical aspects of psychopathology (Berrios, GE and Porter R. *The history of clinical psychiatry*- Athlone Press, London, 1995 and Berrios GE. *Aetiology. In the Great Notions of Psychiatry: A conceptual history*: Oxford University Press, London, 2000).

Minor or neurotic depressions are, in my mind, a misnomer because the so-called minor, which is the opposite of major, may be quite severe and may lead to suicide, while the major or endogenous depression, may have occasionally less severity and may respond better to treatment. Weitbrecht wrote about endoreactive depression, which you mentioned and probably would be equivalent to double depression.

I am sorry for the elimination of neurotic disorders, which are often chronic. You refer to Raskin's "poor premorbid personality." I don't know what "poor" means in this nosological construct. Kurt Schneider listed at least 10 premorbid personalities. I had a colleague in Lima, Peru, who had a hypomanic personality and another in Montreal who had a depressive personality and eventually died of Parkinson's Disease. The DSM-V preserves the three main groupings of personality disorders, namely A: the paranoiac, schizoid and schizotypic; B: the histrionic, narcissistic, anti-social and borderline; and group C: the obsessive-compulsive,



dependent and avoidant. In my mind, many of these disorders blur the boundaries between trait and state, between psychopathology proper and premorbid personality and finally many overlap one with the other.

You did not discuss the issue of combination pharmacological therapy, which Leslie Solyom dared to implement in refractory depression by combining MAOI and tricyclic antidepressants. In Argentina, a well-known psychiatrist in this area is Eduardo Kalina. I, myself, have used combinations of psychopharmacologic agents without complications in refractory depression, which, as you know, are on the rise despite neuropsychopharmacology. I have used escitalopram and duloxetine with excellent results. By the way, in your list of antidepressants, duloxetine is not included. I like the simplicity of Esquirol's classification: lypemania, monomanía and mania which you mentioned.

E. Stengel published (Bulletin World Health Organization 1959; 21:601-63) a monograph on comparative classifications of mental disorders, which was amazing because it included the Russian, Chinese, German, English, French, etc. I don't think that DSM-V is the end of the story. It is quite shocking that Leonhard and Henri Ey were largely ignored in the USA. I heard that they refused a translation into English of Ey's *Études Psychiatriques*, which was published in three volumes by Desclée de Brouwer, Paris, in 1950 with an amazing theoretical and clinical wealth reaching across all national boundaries.

I enjoyed reading your E-Book very much!

March 5, 2015

### **Thomas A. Ban's Reply**

I did not refer to Freud, Kretschmer and to many of the other conceptualizations and classifications of depression because I did not find them relevant to research needed to resolve the pharmacological heterogeneity of depression. If you think they could help identifying subpopulations of depression responsive to pharmacological treatment, please elaborate further. Regardless of their relevance to psychopharmacology, I enjoyed reading the bits of historical information you brought to attention in your comment.

September 10, 2015

