

Mood (Affective Disorders)

ICD-10 Classification

F30 Manic Episodes

- F30.0 Hypomania
- F30.1 Mania without psychotic symptoms
- F30.2 Mania with psychotic symptoms
 - *.20 with mood-congruent psychotic symptoms
 - *.21 with mood-incongruent psychotic symptoms
- F30.8 Other manic episodes
- F30.9 Manic episode, unspecified

F31 Bipolar affective Disorder

- F31.0 Bipolar affective Disorder, current episode hypomanic
- F31.1 Bipolar affective Disorder, current episode manic without psychotic symptoms
- F31.2 Bipolar affective Disorder, current episode manic with psychotic symptoms
 - *.20 with mood-congruent psychotic symptoms
 - *.21 with mood-incongruent psychotic symptoms
- F31.3 Bipolar affective Disorder, current episode mild or moderate depression
 - *.30 without somatic syndrome
 - *.31 with somatic syndrome
- F31.4 Bipolar Affective Disorder, current episode severe depression without psychotic symptoms
- F31.5 Bipolar affective Disorder, current episode severe depression with psychotic symptoms
 - *.50 with mood-congruent psychotic symptoms
 - *.51 with mood-incongruent psychotic symptoms
- F31.6 Bipolar affective Disorder, current episode mixed
- F31.7 Bipolar affective Disorder, currently in remission
- F31.8 Other Bipolar affective Disorder
- F31.9 Bipolar affective Disorder, unspecified

F32 Depressive Episode

- F32.0 Mild depressive episode
 - *.00 without somatic syndrome
 - *.01 with somatic syndrome
- F32.1 Moderate depressive episode
 - *.10 without somatic syndrome
 - *.11 with somatic syndrome
- F32.2 Severe depressive episode without psychotic symptoms
- F32.3 Severe depressive episode with psychotic symptoms
 - *.30 with mood-congruent psychotic symptoms
 - *.31 with mood-incongruent psychotic symptoms

- F32.8 Other depressive episodes
- F32.9 Depressive episode, unspecified

F33 Recurrent depressive disorder

- F33.0 Recurrent depressive disorder, current episode mild
 - *.00 without somatic syndrome
 - *.01 with somatic syndrome
- F33.1 Recurrent depressive disorder, current episode moderate
 - *.10 without somatic syndrome
 - *.11 with somatic syndrome
- F33.2 Recurrent depressive disorder, current episode severe without psychotic symptoms
- F33.3 Recurrent depressive disorder, current episode severe with psychotic symptoms
 - *.30 with mood-congruent psychotic symptoms
 - *.31 with mood-incongruent psychotic symptoms
- F33.4 Recurrent depressive disorder, currently in remission
- F33.8 Other recurrent depressive disorders
- F33.9 Recurrent depressive disorder, unspecified

F34 Persistent mood (affective) disorders

- F34.0 Cyclothymia
- F34.1 Dysthymia
- F34.8 Other Persistent mood (affective) disorders
- F34.9 Persistent mood (affective) disorder, unspecified

F38 Other mood (affective) disorders

- F38.0 Other single mood (affective) disorders
 - .00 Mixed affective episode
- F38.1 Other recurrent mood (affective) disorders
 - .10 Recurrent brief depressive disorder
- F38.8 Other specified mood (affective) disorders

F38 Unspecified mood (affective) disorder

Classification of Affective Disorders

Unipolar vs. Bipolar (Leonhard 1962; Angst, 1966; Perris, 1966)

- Leonhard described 3 different types of affective disorder:
 - *unipolar depression*
 - *unipolar mania*
 - *bipolar*
- *unipolar* - ≥ 3 complete episodes of depression, never manic
 - more common in females
 - episode is longer with somatic symptoms
- *bipolar* - ≥ 1 episode of depression and of mania, or multiple episodes of mania
 - commonly has a seasonal pattern
 - hypersomnia is more common
 - more common in males
 - family history of mania
 - earlier, more acute onset
 - more episodes

Sub-classification of Bipolar Illness

- *Bipolar I* at least one manic episode +/- depression
- *Bipolar II* at least one hypomanic episode + depression
- *Bipolar III* unipolar with bipolar disorder in 1st degree relatives

Endogenous ('melancholia') vs. reactive depression

- *melancholia* refers to severe depression with anhedonia, diurnal variation in mood, lack of reactivity, psychomotor retardation or agitation, early morning wakening, anorexia/ marked weight loss (a.k.a. somatic symptoms in ICD-10)
- research supports continuum viewpoint
- Paykel (1971) suggested 4 groups on the basis of latent cluster analysis:
 1. psychotic depressives
 2. anxious depressives
 3. hostile depressives
 4. younger depressives with personality disorder

The Newcastle School (Roth, 1950s)

- **Endogenous depression**
- characterized by:
 - loss of appetite
 - weight loss
 - constipation
 - reduced libido

- amenorrhoea
- early morning wakening
- psychomotor retardation or agitation
- better response to somatic treatments, e.g. ECT
- poorer response to placebo treatments
- more evidence of neurobiological abnormality

- **Reactive depression**
- characterized by:
 - anxiety
 - irritability
 - phobias
 - initial insomnia
 - persistent reactivity of mood

Bipolar Affective Disorder

Epidemiology

Prevalence

- 1 year = 1.0 % (ECA study)
- Lifetime risk = 0.5-1 % (ECA study)

Demographics

- mean age of onset = 21 years
- 90 % of patients develop the disorder before 50 years of age
- Geographic area:
 - rates are higher in urban areas
- some reports of higher rates in higher social classes
- Sex:
 - M:F = 1:1
 - In Bipolar II disorder, females may predominated
- Marital status:
 - lower rates among married individuals than amongst divorced or never married
 - rate of divorce is three times higher in patients with BAD (Coryell *et al*, 1993)

Associations

- comorbid with:
 - alcoholism
 - cyclothymic personality
 - schizoaffective disorder
 - anxiety states

Aetiology

Genetic causes

- bipolar patients appear to have a greater genetic loading for mood disorder than unipolar patients

Family aggregation studies

- risk of bipolar illness in 1st degree relatives of unipolar illness = 0.6 %
- risk of bipolar illness in 1st degree relatives of bipolar illness = 7.8 %

Twin studies (Bertelson *et al*. 1977)

- MZ : DZ = 79 % : 19 %

Adoption studies (Mendelwicz and Rainer, 1977)

	<i>Parents (% Affected)</i>	
	Biological	Adoptive
<i>bipolar adoptees</i>	28	12
<i>bipolar non-adoptees</i>	26	-
<i>normal controls</i>	5	9

- adopted children of affected biological parents have higher risk
- biological parents of affected adopted children have higher risk
- adoptive parents of affected children have normal risk

Molecular genetics

- RFLP analysis in Amish pedigree suggested possible locus for bipolar depression on the short arm of chromosome 11, region p15 (Egeland *et al.* 1987) – gene for tyrosine hydroxylase (metabolism of NA and DA) known to be located on the short arm of chromosome 11
- other linkage studies have implicated long arm of chromosome X (regions q27 & q28)
- however, these results have not been replicated

Biochemical research

- bipolar patients have lowered levels of MHPG in urine compared to patients with unipolar depression
- reports of normal, or even raised growth hormone response to noradrenergic stimuli (usually blunted in unipolar depression) reflects increased sensitivity of the noradrenergic system

Predisposing life events and life difficulties

- excess of life events preceding depression and also mania (Hunt *et al.* 1992)

Diagnostic Criteria

A disorder characterized by two or more episodes in which the patient's mood and activity levels are significantly disturbed, this disturbance consisting on some occasions of hypomania or mania, and on others, depression. Repeated episodes of hypomania or mania only are classified as bipolar.

Hypomanic Episode

- A. The mood is elevated or irritable to a degree that is definitely abnormal for the individual concerned and sustained for at least 4 consecutive days
- B. At least three of the following signs must be present, leading to some interference with personal functioning in daily living :
 1. increased activity or physical restlessness
 2. increased talkativeness

3. difficulty in concentration or distractability
4. decreased need for sleep
5. increased sexual energy
6. mild overspending, or other types of reckless or irresponsible behaviour
7. increased sociability or overfamiliarity

Manic Episode

- A. Mood must be predominantly elevated, expansive or irritable, and definitely abnormal for the individual concerned. The mood change must be prominent and sustained for at least 1 week (unless it is severe enough to require hospital admission)
- B. At least three of the following signs must be present (four if the mood is merely irritable), leading to severe interference with personal functioning in daily living :
 1. increased activity or physical restlessness
 2. increased talkativeness
 3. flight of ideas or the subjective experience of thoughts racing
 4. loss of normal social inhibitions, resulting in behaviour that is inappropriate to the circumstances
 5. decreased need for sleep
 6. inflated self-esteem or grandiosity
 7. distractibility or constant changes in activity or plans
 8. behaviour that is foolhardy or reckless and whose risks the individual does not recognize, e.g. spending sprees, foolish enterprises, reckless driving
 9. marked sexual energy or sexual indiscretions

Different Types of Bipolar Illness

- relatives of bipolar I patients are more likely to have bipolar I disorder, and relatives of bipolar II patients are more likely to develop bipolar II disorder

Bipolar I

- presence of at least one episode of mania, or mixed mania and depression
- in most cases the manic episode occurs in someone who already has a history of major depression
- there is a tendency in bipolar I disorder for episodes to recur more frequently as the illness progresses, with shorter illness-free periods
- onset is much younger than unipolar depression

Bipolar II

- generally not as serious as bipolar I
- recurrent depression and episodes of hypomania, but **no** episodes of mania
- more chronic course for bipolar II (higher rates of alcoholism and other comorbid disorders)
- may have more frequent relapses into depression

Rapid cycling Bipolar Disorder

- *rapid cycling* was coined by Dunner & Fieve (1974)
- they arbitrarily defined rapid cycling as four or more mood episodes per year
- episodes are demarcated by a switch to an episode of opposite polarity or by a period of remission
- may occur in up to 20 % of patients, although in 50% of patients rapid-cycling lasts less than two years
- tends to develop late in the course of illness (*kindling, sensitization*)
- more common in women
- generally predicts a worse prognosis and lithium resistance
 - usually (80 %) patients are LITHIUM-resistant
- CARBAMAZEPINE or VALPROATE are useful agents of choice (Calabrese *et al.* 1995)
- **Risk factors:**
 1. Alcohol and substance misuse
 - Alcohol misuse increases the frequency of relapse in patients with BAD, possibly inducing rapid cycling
 2. Antidepressants:
 - history of antidepressant-induced mania
 - previous rapid cycling
 3. Lithium
 - Approx 50% of patients who develop biochemical or symptomatic hypothyroidism whilst taking lithium are at an increased risk for rapid cycling
 4. Hypothyroidism
 - A number of studies have suggested that hypothyroidism is more common in rapid- than in non-rapid-cycling bipolar patients
 5. Other Medical Conditions:
 - sub-arachnoid haemorrhage
 - CVA
 - multiple sclerosis
 - head injury
 - gonadal steroid (e.g. oestrogen)
 - drugs (PROPANOLOL, L-DOPA, CYPROHEPTADINE)

Treatment

1. 72-82% of rapid-cycling patients show a poor response to LITHIUM (Dunner & Fieve, 1974)
2. rapid cycling patients treated with CARBAMAZEPINE exhibit an acute response rate of 32% for depression and 52% for mania. The prophylaxis response rate for CARBAMAZEPINE is 57% for depression, and 59% for mania.
3. VALPROATE has marked acute and prophylactic antimanic effects, but only mild to moderate acute and prophylactic antidepressant effects. Predictors of response are:
 - Absence of psychotic features
 - Absence of borderline personality disorder
 - Presence of mild – moderate hypomania or mixed affective symptoms

4. CLOZAPINE, due to its action at D4 receptors (occur at high density in the limbic system) may have a mood stabilising action

Mixed Affective states

- during transition from mania to depression and vice versa, Kraepelin held that mood, cognition, and behaviour may vary independently, producing 'mixed' states
- there are six combinations :
 1. *manic stupor* (elation, increased thought tempo, motor retardation)
 2. *excited (agitated) depression* (decreased thought, depressed mood, overactivity)
 3. *anxious mania* (increased thought tempo, overactivity, anxious mood)
 4. *unproductive mania* (decreased thought tempo, overactivity, elation)
 5. *depression with flight of ideas* (depressed mood, motor retardation, increased thought tempo)
 6. *inhibited mania* (decreased thought tempo, motor retardation, elation)
- some studies suggest that up to 30 % of bipolar patients present with mixed symptoms in first episode (Himmelhoch *et al.* 1976)
- most patients show subthreshold, long-lasting symptomatology
- they may have more variability and lability in mood
- more likely to have a history of drug abuse

Treatment of Bipolar Affective Disorder

Lithium

- treatment of mania (3-4 days for therapeutic effect) – 75 % response rate
- reported to have a beneficial effect in reducing suicide risk:
 - naturalistic studies have reported that lithium treatment reduces the suicide risk by 5 times
 - a doubling in the suicide attempt rate in the first year may follow withdrawal of lithium
- there is evidence of loss of efficacy during prolonged treatment (also reported with carbamazepine, and to a lesser extent with valproate)

Carbamazepine

- response rate in mania is 65 % (i.e. less than LITHIUM)
- generally used as 2nd line drug for treatment / LITHIUM resistance or LITHIUM intolerance
- possible failure of prophylaxis after four years

Valproate

- 3rd line treatment in mania

- patients with mixed affective disorder may do better than those with ‘pure’ mania (McElroy *et al.* 1992)
- more effective at preventing mania than depression

Other drugs

- CLOZAPINE has recently been shown to be effective in mania

Indications for maintenance therapy

Bipolar I	3 episodes of depression or mania, regardless of interval
	2 episodes of depression or mania within 5 years
	2 episodes in those with either positive family history of bipolar I or severe illness
Bipolar II	3 episodes of depression or hypomania, regardless of interval
	2 episodes of depression or hypomania in 5 years

- Note that some clinicians consider the above guidelines too stringent, denying the patient of treatment
- Many feel that a *single episode of full-blown mania* occurring at an *early age* with a *positive family history* is sufficient indication for long-term prophylactic treatment

Predictors of Response

1. Lithium

- a) good premorbid personality
- b) low neuroticism
- c) good interepisode functioning
- d) family history of lithium response
- e) family history of bipolar disorder
- f) non-rapid cycling

2. Valproate

- a) rapid cycling illness
- b) dysphoric mania (mixed states)
- c) closed head injury
- d) EEG abnormalities
- e) learning disability
- f) later age of onset
- g) shorter duration of illness

Predictors of lithium non-response

1. mixed or dysphoric mania
2. rapid cycling
3. a depression-mania-well sequence
4. substance misuse comorbidity

Discontinuation of therapy

- 50 % of people relapse within 5 months if LITHIUM is stopped
- slow discontinuation reduces the risk of relapse, although the benefit is lost after the first year
- it has been suggested that discontinuation of lithium results in patients developing a more resistant form of the illness than they had hitherto suffered (Post *et al*, 1992)

Outcome

- poor outcome associated with:
 1. poor compliance
 - 75 % of relapses are due to poor compliance
 2. mixed affective states
 3. rapid cycling
 4. chronic depression
 5. severe mania
 6. family history of non-response

Depressive illness

Epidemiology

Incidence and Prevalence

- one-month prevalence rate (ECA Study, Regier *et al.* 1988) = 1.6 per 100 males and 2.9 cases per 100 females (overall 2.2 %)
- lifetime prevalence of 5.8 % (ECA Study)
- 70 % of women and 40 % of men have experienced clinically significant depressive symptoms by the age of 65
- depressive symptoms common, 13-20 % point prevalence (Boyd & Weissman, 1982); more common in:
 - women
 - lower socioeconomic groups
 - divorced/ separated
- ECA study found that the highest 1 year prevalence for major depression was in the 18-44 age group and that lifetime prevalence actually decreased with age :
 - *period effect* – rate change is associated with period of time during which disease onset occurs
 - *birth-cohort effect* – rate change is associated with period of time subject was born (Klerman, 1988)

Demographics

- M:F = 1:2 (*c.f.* bipolar disorder 1:1)
- mean age of onset = 27 (ECA data)
- women have peak onset in 30s, males in 40s
- Weissman and Myers (1978) found increased rate of depression in lower socio-economic groups
- higher prevalence in lower social group females (Brown and Harris, 1978)
- ECA study found rates of depression were 3 times higher in the unemployed and welfare receivers
- no evidence of ethnic variation in UK – ethnic differences in US appear more related to social class difference
- marital status :
 - highest in divorced / cohabiting
 - low rates in never married
 - lowest rates in married, and never divorced
- geographic area :
 - urban > rural, but not unequivocally
 - industrialized countries
 - higher rates reported in Europe (prevalence of 16 %)
- higher rates in the unemployed
- recent research postulates significant association between smoking and depression (Breslau *et al.* 1993; Kendler *et al.* 1993)

Aetiology

Genetic causes

Family vulnerability to depression

- early onset
- long duration of episodes
- high levels of impairment
- recurrent thoughts of death or suicide

Family aggregation studies

- risk of unipolar depression in 1st degree relatives of unipolar illness = 9 %
- risk of unipolar depression in 1st degree relatives of bipolar illness = 11.4 %
- overall risk of mood disorder in 1st degree relatives is 20 %

Twin studies (Bertelson *et al.* 1977)

- MZ: DZ = 54 %:24 %

Adoption studies

- studies of adoptees also support genetic theories

Molecular genetics

- genetic linkage and association studies on colour blindness (X-chromosome determined) or other candidate markers have shown no positive findings
- other genes implicated:
 - insulin gene (chromosome 11)
 - cellular oncogene *Ha-ras-1* (chromosome 11)

Possible modes of transmission

- *polygenic* –may explain continuum of severity and heterogeneity
- *Autosomal dominant* - suggested by uniform morbidity risk among parents, children and siblings; incomplete penetrance might account for less than 100 % concordance in MZ twins

Personality

- the most relevant personality features are obsessional traits and readiness to develop anxiety
- *neuroticism* as assessed on the Eysenck Personality Questionnaire may predispose to major depression

Early Environment

Parental loss

- psychoanalysts have suggested that deprivation of maternal affection through separation or loss predisposes to depressive disorders in adult life, but this is not supported by epidemiological studies
- there is more evidence that depressive illness in later life is associated with *parental separation*; the main factor appears to be *parental discord*

Parental style

- the two most consistently generated dimensions of parental style are *lack of care* and *overprotection* (Parker 1979)

Childhood abuse

- is a risk factor for later depression

Precipitating factors

Recent life events

- 70 % of depressive episodes are preceded by life events
- there is an excess of life events in the months before the onset of depressive illness (Paykel *et al.* 1969; Brown and Harris 1978) – also seen in suicide, schizophrenia, and neurosis
- Paykel found that the risk of developing depression increased sixfold in the six months after experiencing markedly threatening life events
- the strongest relationship between life events and depression is with events that can be categorized in a general way as *threatening* or *undesirable*

Predisposing life events and life difficulties

- Brown and Harris (1978) studied working-class women in Camberwell, London and found particular circumstances acting as vulnerability factors :
 1. three or more children under the age of 15 at home
 2. not working outside the home
 3. having no-one to confide in / unsupportive relationship with husband
 4. loss of the mother by death or separation before the age of 11
 5. excess of threatening life events or major difficulties prior to onset of depression
- only 1 and 3 have been confirmed in other studies
- subsequent studies (Brown *et al.* 1986; Surtees *et al.* 1986) only partly replicated the above hypothesis, and also suggest that *low self-esteem* is a major vulnerability factor
- excess of life events preceding depression and also mania (Hunt *et al.* 1992)
- poor social support (lack of intimacy or social integration) is associated with an increased risk of depression

Anaclitic depression

- coined by Spitz in 1946
- describes a condition of misery, crying, withdrawal, and failure to thrive in babies and young children suffering from severe deprivation of parental care
- seen in large, poorly-run institutions

Psychological Theories of Depression

Psychoanalytical theory

- **Freud (1917)** suggested that melancholia results from *loss* - the loss of an 'object'
 - depression was thought to occur when feelings of love and hostility were present at the same time (*ambivalence*)
- **Abraham (1920)** – depression results from loss of the love object
 - proposed that the depressed patient regresses to an earlier stage of development
- **Klein (1934)** suggested that if the 'depressive position' was not passed through successfully, the child will be more likely to develop depression when faced with loss in adult life
- mania is seen as a defence against depression

Cognitive/ Behavioural theories

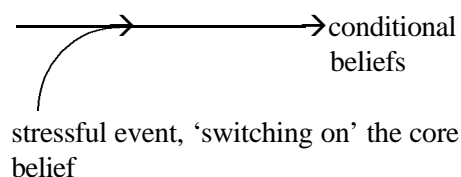
- **Wolpe** – depression conditioned by repeated losses in the past
- **Seligman (1975)** proposed that depression results when 'highly desirable outcomes are believed improbable or highly aversive outcomes are believed probable and the individual expects that no response (of his) will change their likelihood' – *learned helplessness*
- **Beck (1967)** :
- 3 main concepts :

A. Cognitive Distortions

1. *arbitrary inference* = conclusions in absence of evidence
2. *overgeneralisation* = conclusion formed on basis of one incident
3. *selective abstraction* = person abstracts from whole situation and focuses on a single incident
4. *personalisation* = relating external events to oneself
5. *magnification/ minimization* = errors in evaluation
6. *dichotomous reasoning* = 'all-or-nothing' thinking

B. Latent Maladaptive Schemata

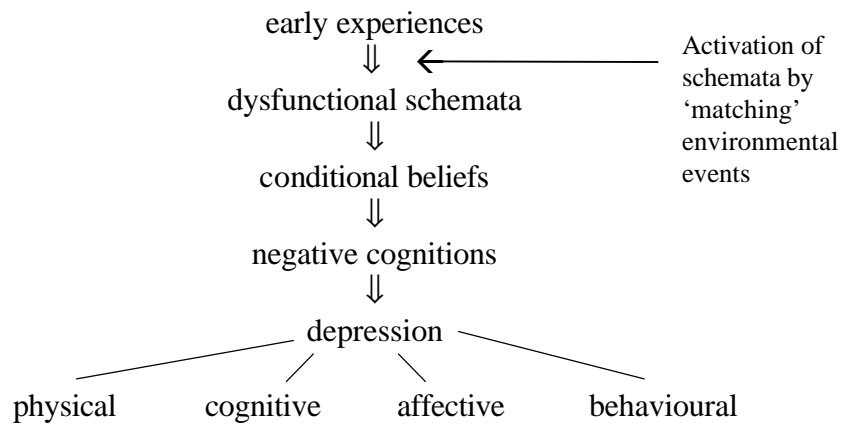
- a.k.a. negative core beliefs
- based on *stress-diathesis model* :
 - latent maladaptive beliefs



- depressed people interpret stimuli so that it is consistent with their underlying beliefs

3. Negative Cognitive Triad

1. negative view of oneself (worthless, inadequate)
2. negative view of the world (overwhelming, demanding)
3. negative view of the future (hopeless, unchangeable)



Biochemical Theories

Monoamine Hypothesis

- suggest that depressive disorder is due to an abnormality in a monoamine neurotransmitter system at one or more sites in the brain

5-HT Function

- *Decreased* :
 - plasma tryptophan concentration
 - platelet 5-HT uptake
 - 5-HIAA level in CSF (suicide victims); no decrease in brain levels of 5-HIAA
 - ³H-imipramine binding in platelets, in frontal cortex, and in hippocampus
 - blunted 5-HT₁ mediated prolactin response (Cowen and Charig, 1987)
 - the prolactin response to *L*-TRYPTOPHAN and CLOMIPRAMINE is consistently reduced in depressed patients, while the response to FENFLURAMINE is lowered in most studies
 - recovery results in the responses returning to normal
- *Increased* :
 - increased cortical post-synaptic 5-HT₂ receptors (suicide victims)
 - 5-HT₂ receptor binding in platelets

Noradrenaline Function

- *Decreased* :
 - NA-mediated growth hormone release in response to DESIPRAMINE (NA re-uptake inhibitor) and CLONIDINE (NA receptor agonist)
 - platelet CAMP turnover with stimulation by CLONIDINE
 - ? decreased responsiveness of postsynaptic α_2 -adrenoceptors (in hypothalamus)
- *Increased* :
 - platelet alpha-2-adrenergic-receptor binding
 - β -adrenergic receptors in suicides

Dopamine Function

- *Decreased* :
 - homovanillic acid (HVA) levels in CSF of depressed patients

Acetylcholine function

- little evidence, apart from cholinergic basis for sleep disturbances in affective disorder, findings which are consistent with postsynaptic muscarinic supersensitivity

Neuropeptides

- decreased CSF somatostatin and neuropeptide

Neuroendocrine abnormalities

Hypothalamic-Pituitary-adrenal axis

- in 50% of patients with a moderate-severe depressive illness, plasma cortisol is increased throughout the 24 hour cycle – loss of circadian rhythm
- 50 % of depressed in-patients do not show the normal suppression of cortisol induced by 1 mg of DEXAMETHASONE (DEXAMETHASONE suppression test) (Carroll *et al.* 1976) – also seen in schizophrenia and dementia
- increased cortisol response to ACTH, increased number of ACTH secretory episodes
- blunted response to CRH
- abnormalities in cortisol regulation in depression can be explained by **hypersecretion of CRH in the hypothalamus** with a resultant increase in ACTH and cortisol release
- CRH has a neurotransmitter role in limbic regions of the brain where it is involved in regulating biochemical and behavioural responses to stress
- there is also hypercortisolaemia in mania, with a loss of the usual p.m. spike

Thyroid Function

- thyroxine levels are normal, but levels of free T₃ may be reduced
- blunted TSH response to intravenous TRH (25 % of patients)

Electrolyte disturbance

- ‘residual sodium’ has been reported to be increased in both mania and depression
- active transport of sodium and potassium increases on recovery from mania and depressive disorders
- erythrocytes of drug-free manic patients have increased sodium pump activity

Psychoimmunology

- decreased natural killer cells
- decreased T-cell replication
- decreased interleukin-2
- increased monocyte activity
- immune deficits may be related to H-P-A axis dysfunction – modulated through type II glucocorticoid receptors in limbic system (Maes *et al.* 1993)

Sleep changes in depression

- EEG shows :
 - impaired sleep continuity and duration
 - decreased deep sleep (stages 3 and 4)
 - decreased latency to the onset of REM sleep
 - increase in proportion of REM sleep in the early part of the night
- EEG changes may persist in recovered depressed patients and indicate a vulnerability to relapse
- many antidepressant drugs decrease REM sleep time and its latency to onset
- sleep deprivation and selective REM sleep deprivation can result in a temporary alleviation of mood in 30-60 % (melatonin may be involved)
- may be attributable to excessive sensitivity of muscarinic cholinergic receptors

Brain imaging in depression

- CT and MRI shows *enlarged lateral ventricles* but the data are inconsistent
- there may be a correlation between enlarged ventricles and cognitive impairment
- MRI shows :
 - loss of volume in temporal and frontal lobes in some studies
 - reduction of caudate nucleus size
- PET :
 - decreased blood flow in the *dorsolateral prefrontal cortex, the cingulate cortex*, and perhaps some regions of the *basal ganglia* (Bench *et al.* 1991)

Diagnostic Criteria

- A. The depressive episode should last at least 2 weeks
- B. There have been no hypomanic or manic symptoms sufficient to meet the criteria for hypomanic or manic episode at any time in the individual's life

Somatic Syndrome

A fifth character may be used to specify the presence or absence of the somatic syndrome. To qualify for the somatic syndrome, four of the following symptoms should be present :

1. marked loss of interest or pleasure in activities that are normally pleasurable
2. lack of emotional reactions to events or activities that normally produce an emotional response
3. waking in the morning 2 hours or more before the usual time
4. depression worse in the morning
5. objective evidence of marked psychomotor retardation or agitation (remarked on or reported by other people)
6. marked loss of appetite
7. weight loss (5 % or more of body weight in the past month)
8. marked loss of libido

F32.0 Mild depressive episode

- A. The general criteria for depressive episode must be met
- B. At least two of the following three symptoms must be present :
 1. depressed mood to a degree that is definitely abnormal for the individual, present for most of the day and almost every day, largely uninfluenced by circumstances, and sustained for at least 2 weeks
 2. loss of interest or pleasure in activities that are normally pleasurable
 3. decreased energy or increased fatigability
- C. An additional symptom or symptoms from the following list should be present, to give a total of at least four :
 1. loss of confidence or self esteem
 2. unreasonable feelings of self-reproach or excessive and unreasonable guilt
 3. recurrent thoughts of death or suicide, or any suicidal behaviour
 4. complaints or evidence of diminished ability to think or concentrate, such as indecisiveness or vacillation
 5. change in psychomotor activity, with agitation or retardation (either subjective or objective)
 6. sleep disturbance of any type
 7. change in appetite (decrease or increase) with corresponding weight change

F32.1 Moderate depressive episode

- A. The general criteria for depressive episode must be met
- B. At least two of the three symptoms listed for F32.0, criterion B, must be present

- C. Additional symptoms from F32.0, criterion C, must be present, to give a total of at least six

F32.2 Severe depressive episode without psychotic symptoms

- A. The general criteria for depressive episode must be met
- B. All three symptoms in criterion B, F32.0, must be present
- C. Additional symptoms from F32.0, criterion C, must be present, to give a total of at least eight
- D. There must be no hallucinations, delusions, or depressive stupor

F32.3 Severe depressive episode with psychotic symptoms

- A. The general criteria for depressive episode must be met
- B. The criteria for severe depressive episode without psychotic symptoms (F32.2) must be met with the exception of criterion D
- C. The criteria for schizophrenia or schizoaffective disorder, depressive type are not met
- D. Either of the following must be present :
 1. delusions or hallucinations, other than those listed as typically schizophrenic (i.e. delusions other than those that are completely impossible, or culturally inappropriate, and hallucinations that are not in the 3rd person or giving a running commentary); the commonest examples are those with depressive, guilty, hypochondriacal, nihilistic, self-referential or persecutory content
 2. depressive stupor

Treatment

Psychosocial Interventions

- minimize adverse life events, e.g. financial hardship, housing difficulties, etc.
- promote secure, confiding relationship (Cox, 1993)

Psychotherapy

- *Cognitive behavioural therapy (CBT)* :
 - systematic treatment aimed at challenging ‘logical errors’, ‘automatic negative thoughts’ and ‘generalizations’
 - effective in acute treatment of less severe, non-melancholic depression (NIMH Treatment of Depression Collaborative Research Program – Elkin *et al.* 1989)
 - needs to be at least 16-week duration, and appears to be as effective as pharmacotherapy in reducing later relapse (Evans *et al.* 1992)
 - no consensus that combined CBT plus medication is better than either modality singly (Hollon *et al.* 1992)
- *Interpersonal therapy (IPT)* :

- exploration of origins of depression in terms of interpersonal losses, role disputes and transitions, social isolation, deficits in social skills
- effective in acute treatment of depression, particularly for vocational and social sequelae of illness (Frank *et al.* 1991)

Antidepressants

- MRC trial, 1965 :

<i>Tricyclics</i>	<i>MAOIs</i>	<i>Placebo</i>
50-60 % recovery	33 % recovery	30 % recovery

- patients with *recurrent* depressive illness should receive long-term maintenance therapy at the dose that produced the initial response (Kupfer *et al.* 1992) – benefit even at 5 years after index episode
- claims for superiority of an individual antidepressant are unsubstantiated
- MAOIs best used for ‘atypical depression’, not generally used as 1st line treatment

Combination therapies

- SSRI + Trazodone
- SSRI + TCA
- TCA + MAOI
- addition of low-dose lithium to standard TCA regime will augment effect
- neuroleptics given in combination with TCAs are more effective than either singly in treating ‘psychotic’ depression

ECT

- effective in 50 % of drug-resistant patients
- most relapse within a year

Psychosurgery

- 2/3 of depressives treated with limbic leucotomy are reported to improve

Other presentations of depressive illness

Agitated depression

- more common in:
 - middle-aged
 - elderly

Retarded depression

- predicts good response to ECT

Masked depression

- more likely with mild or moderate illness

Atypical (masked) depression

- illness presenting as either :
 1. physical conditions
 2. non-affective psychiatric disorders
- characterized by:
 - mood reactivity
 - overeating
 - oversleeping
 - 'leaden paralysis'
 - 'rejection sensitivity'
- chronic pain, hypochondriasis, psychosomatosis, conversion disorders – usually show absence of significant organic pathology, poor response to medical treatment and some depressive features
- pseudodementia, anxiety states, behavioural change (e.g. shop-lifting in middle-aged women)
- has a better response to MAOIs

Brief recurrent depression

- unclear boundaries with dysthymia
- no link to menstrual cycle
- risk of mania is low

Bereavement reactions

The Symptomatology of normal grief

- normal grief has 3 phases:
 1. stunned (shock) phase (few hours to 2 weeks)
 2. mourning (pining) phase (lasts for several weeks)
 3. acceptance and adjustment
- initial shock and disbelief – 'a feeling of numbness'

- increasing awareness of the loss is associated with painful emotions of sadness and anger
- anger may be denied
- irritability
- somatic distress:
 - sleep disturbance
 - tearfulness
 - loss of appetite
 - weight loss
 - loss of libido
 - anhedonia
 - early morning wakening
- identification phenomena – in which the mannerisms and characteristics of the deceased person may be taken on
- preoccupation with deceased
- transient hallucinatory phenomena

- may involve:
 - projection
 - wish fulfillment
 - denial
 - introjection
 - identity diffusion

Atypical/ Morbid grief (Parkes, Lindemann)

- guilt about things other than actions taken or not taken by the survivor at the time of the death
- thoughts of death other than the survivor feeling that he or she would be better off dead, or should have died with the deceased person
- morbid preoccupation with worthlessness
- marked psychomotor retardation
- prolonged and marked functional impairment
- hallucinatory experiences other than thinking that he or she hears the voice of, or transiently sees the image of, the deceased person
- delayed reaction
- ‘mummification’ – e.g. still laying place setting long after death/ room exactly as left
- ‘stuckness’ – person appears unable to move on, or accept the loss after a reasonable amount of time
- atypical grief is divided by Parkes (1985) into:
 1. unexpected grief syndrome
 2. ambivalent grief syndrome
 3. chronic grief

Cyclothymia

Demographics

- prevalence = 1 %
- M:F = 1:1
- onset 15-25 years

Clinical features

- less severe mood disturbance, persistent instability of mood, less chronic course
- common in relatives of patients with major affective disorder
- some patients in middle age eventually develop major affective disorder superimposed on cyclothymia
- 33 % will develop bipolar affective disorder
- treated with antimanic agents

Dysthymia

Demographics

- lifetime prevalence = 3 %
- higher rates in:
 - women
 - unemployed
- onset before the age of 25

Aetiology

- associated with:
 - loss of close relative
 - chronic medical illness

Clinical features

- equated in ICD-10 and DSM-IV to chronic, low grade, 'neurotic' depression which is rarely severe enough to fulfill the criteria for recurrent depressive disorder (mild or moderate)
- frequently complicated by superimposed major depressive episodes – '*double depression*'
- boundaries between dysthymia, chronic unremitting major depression, and depressive personality traits are controversial

Treatment

- antidepressants (particularly SSRIs)
- CBT
- Insight-oriented therapy

Outcome

- 20 % go on to suffer a major depressive episode

- 20 % go on to develop bipolar disorder

Seasonal Affective disorder (SAD)

Epidemiology

- females > males (may be a selection bias)
- true prevalence unknown – 4 % of population in Washington, USA had winter SAD (Kasper *et al.* 1989)

Aetiology

- pathophysiology unknown – dysregulation of melatonin postulated
 1. melatonin deficit
 2. 'phase shift' in normal circadian output of melatonin
 3. dopamine-mediated abnormality in melatonin secretion

Clinical features

- 'atypical' depressive features – anxiety, irritability, increased fatigue, **increased sleep, increased appetite**, weight gain ('**carbohydrate craving**')
- onset usually in autumn or winter
- mild hypomania often experienced in summer

Diagnostic guidelines

- history of major affective disorder with at least 3 previous winter depressive episodes
- onset and remission of each depressive episode occur within specific 60-day periods of each other
- absence of clear-cut seasonally changing psychosocial variable

Course and Prognosis of affective disorders

Bipolar Illness

- depression tends to present first, with onset of mania after the age of 30
- manic episodes usually begin abruptly and last from 2 weeks to 5 months (median = 3-4 months)
- more than 50 % of episodes last less than one month with treatment
- depressive episodes tend to last longer (median = 6 months)

Number of episodes

- median number of episodes = 9 (Angst, 1978)
 - 84% had had more than 5
 - 69% had had more than 7
 - 42% had had more than 9
- interepisode interval = 6-9 months
- frequency of episodes seems to increase in the first 10 years, before ceiling
- early relapse seems more likely amongst older onset patients
- patients with mixed affective states seem to have a poorer short-term outcome
- in patients with repeated manic attacks, the length of each episode does not seem to alter in later attacks (average duration of under 3 months)
- patients with bipolar disorder have more episodes of illness than unipolar patients
- manic and depressive episodes are equally frequent in men, but depressive episodes predominate in women
- a family history of mania increases the risk of multiple episodes in bipolar patients
- bipolar depression is more likely to show a seasonal pattern of mood variation than unipolar depression

Impact on life (Scott, 1995)

- individuals developing bipolar illness in their 20's may lose:
 - 9 years of life
 - 12 years of good health
 - 14 years activity

Unipolar depressive illness

- age of onset later than for bipolar illness
- generally 5-6 episodes over 20 years
- the frequency and length of episodes increases with age
- 90 % recover
 - 25 % of patients with depression have recurrence within a year
 - 75 % have a recurrence in 10 years
- 10 % of patients remain persistently depressed after an index episode and have a chronic, unremitting course
- 5 - 10 % of patients will eventually have a manic episode and develop bipolar disorder
- 70 % are correctly diagnosed by 3 episodes (83 % by 6 episodes)

- possible risk factors for bipolar disorder are :
 - young age
 - psychomotor retardation
 - guilt
 - high familial loading for affective disorders
 - family history of mania
 - psychotic symptoms
 - postpartum depression
 - hypomania after drug therapy
- recurrence is associated with female sex and early age of onset
- mood incongruent delusions indicate a worse prognosis

Mood disorders and suicide

- risk of suicide in those with depressive disorder is 30 times the normal population
- 11-17 % of patients who have had a severe depressive illness will eventually commit suicide
- highest risk period is 1-2 years after hospitalization
- 90 % of completed suicides suffer with depression at some time

- it is estimated that 25-50% of those with bipolar disorder will make a suicide attempt at some time (Goodwin & Jamison, 1990)

Bipolar-Unipolar distinction

	Bipolar	Unipolar (recurrent depressive disorder)
Lifetime prevalence	1.2	3-6
Sex ratio (F:M)	1:1	2:1
Mean age of onset	21	27
Social class skew	No	?
MZ : DZ ratio	5:1	2.3:1
Morbid risk of bipolar disorder in 1° relatives	8 %	3 %
Morbid risk of unipolar disorder in 1° relatives	15 %	17 %
Morbid risk of any affective disorder in 1° relatives	23 %	20 %