Ministry of Defence

Synopsis of Causation

Depressive Disorder

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

1.1. **Depression** is a term used in psychiatry to describe a range of mood disorders. The diagnosis of a depressive disorder depends upon the presence of a cluster of depressive symptoms. The nature and severity of these may vary, and this heterogeneity is reflected in a wide range of diagnostic categories.

1.2. In some cases episodes of depression are interspersed with periods of pathologically elevated mood, in which case a diagnosis of **bipolar disorder** is made. This is a distinct entity, and is not the focus of this synopsis, which concentrates on cases in which the patient suffers from depressive symptoms only – often referred to as **unipolar disorder**.

1.3. Cases of unipolar depression may occur as a single lifetime event, be recurrent, or become chronic. An **acute depressive episode** may be diagnosed when symptoms have been present for at least two weeks, and a single episode may persist for up to two years. If symptoms are present continuously for two years or more, a diagnosis of **chronic depression** is made. The majority of those who recover from a depressive episode will eventually suffer a recurrence and hence most depressive episodes form part of a **recurrent depressive disorder**. Whilst a first episode is often precipitated by a negative life event, subsequent episodes may lack an obvious external stimulus. Overall 50-70% of depressive episodes follow a negative life event, although the link between stress and depression becomes less strong with further recurrences.

1.4. Diagnosis of a **depressive episode** involves the identification of a number of symptoms and signs from the list below:

- Depressed mood for most of the day, nearly every day
- Markedly diminished interest or pleasure in all, or almost all, activities, for most of the day, almost every day (as indicated by either subjective account or observation by others)
- Loss of energy, or fatigue, nearly every day
- Loss of self-esteem or confidence, or feelings of worthlessness
- Unreasonable feelings of self-reproach, or excessive or inappropriate guilt, nearly every day
- Recurrent thoughts of death or suicide, or any suicidal behaviour
- Diminished ability to think or concentrate, or indecisiveness, nearly every day
- Psychomotor agitation or retardation nearly every day
- Insomnia or hypersomnia, nearly every day. In most cases, insomnia will be present, with early morning awakening (at least 2 hours before the usual time of awakening)
- Change in appetite (decrease or increase) with a corresponding weight change of more than 5% of body weight per month[1]

1.5. The classification of the depressive disorders is complex. Efforts have been made to establish valid diagnostic categories (mainly in order to facilitate the standardisation of terms used in research). This has resulted in two broadly similar classificatory systems. The first of these, the International Classification of Diseases Version 10 (ICD 10), was developed by the World Health Organisation. The second system, the Diagnostic and Statistical Manual: Mental Disorders Version 4 (DSM IV), is produced by the American Psychiatric Association. Whilst the principal diagnostic features outlined above are used by both systems, the manner in which they are used to classify the depressive disorders is significantly different.

1.6. In DSM IV, the main diagnostic category is major depressive disorder. For this diagnosis to be made, the patient must be suffering from at least 5 of the above symptoms. At least one of these symptoms must be either 'depressed mood' or 'diminished interest or pleasure in activities'. The symptoms should not be attributable to the effects of a general medical condition, nor to the physiological effects of a substance, including drugs of abuse, or prescribed medications. The symptoms must be associated either with significant levels of distress or with functional impairment in social, occupational, and other spheres of activity. Once a diagnosis of major depressive disorder has been established, the DSM IV system then uses 'specifiers' to describe particular features of the illness to categorise it more accurately. Examples of specifiers include 'psychotic features' and 'melancholic features'.

1.7. Classification according to ICD 10 distinguishes three 'typical' symptoms of depression (depressed mood, loss of interest or pleasure, and loss of energy) from the other symptoms outlined above. This system also puts more weight on the severity of a depressive episode, which can be categorised as mild, moderate or severe. A mild episode, for example, requires the presence of two of the 'typical' symptoms, plus two of the other symptoms. A severe depressive episode entails the presence of all three 'typical' symptoms and at least four of the others.

1.8. Despite these differences, the two systems share an important unifying approach to classification of mental disorders. That is, they both categorise the disorders according to descriptive features of the illness, rather than causative factors.

2. Clinical features

2.1. Major depression affects between 10 and 20 people per 100 over a lifetime, and may present at any time of life. However, recent studies have shown that rates of depression are increasing, and that this is associated with an increasingly early age of onset.[2] Women are approximately twice as likely to develop major depression during their lifetime, compared with men. The increased rate in females develops around the time of puberty, and is persistent throughout adult life, though perhaps less marked in the elderly. Major depression is currently the fourth leading cause of disease burden in the world, and it is projected that by 2020 it will be the second.[3]

2.2. A diagnosis of major depression may be accompanied by the specification of particular features of the illness, which identify it as a particular sub-type of major depression. Some of the most important of these, which are outlined in DSM IV, include the following:

2.2.1. **Major depressive episode with atypical features** may be diagnosed if the mood temporarily brightens in response to positive events or interactions ('preserved mood reactivity') and is associated with profound fatigue and a sensation of heaviness in the limbs: 'leaden paralysis'. Such patients often exhibit an increase in sleep and appetite, rather than the insomnia and loss of appetite which is more typical of classical depression.[4]

2.2.2. **Major depressive episode with melancholic features** refers to a patient who gains no relief from activities or interactions which would normally be pleasurable. There is often an absence of emotion or inability to feel rather than the usual low mood or pervasive sadness. The depressive symptoms are generally worse in the morning, and are associated with early morning wakening, loss of appetite, and weight loss. These patients may experience marked psychomotor retardation or agitation, and extreme feelings of inappropriate guilt. These patients may have experienced a good response to drug treatments, during previous episodes.

2.2.3. **Major depressive episode with psychotic features** is a severe presentation of depression in which the patient experiences symptoms which are more typical of a psychotic disorder. The psychotic features are predominantly 'mood congruent', representing an extreme presentation of negative beliefs. Thus, some patients suffer from delusional ideas focusing on themes such as guilt, personal inadequacy, nihilistic ideas and death. For example they may insist that they have somehow harmed others. Alternatively, they may develop paranoid or hypochondriacal beliefs, such as a conviction that they are threatened by others, that they are dead, or that part of their body is decomposing. More rarely, psychotic depressed patients may exhibit psychotic symptoms which are not mood congruent, such as thought broadcasting and thought insertion. In these cases, it may be difficult to differentiate between a schizophreniform illness and depression. See the Synopsis of Causation on the subject of schizophrenia. In some rare cases the patient may fulfil criteria for both depression and a schizophreniform illness, either simultaneously or sequentially, in which case a diagnosis of schizoaffective disorder may be made.

2.3. Some forms of depression are notable for the fact that they follow a particular temporal course, or affect specific populations. These include the following:

2.3.1. **Seasonal depression**, also known as Seasonal Affective Disorder, is a form of recurrent depression which affects 1-3% of adults in temperate climates. Episodes of depression in the relevant season (usually winter) outnumber episodes at other times of the year. There are often features of atypical depression; thus, these patients often crave carbohydrates, over-eat, and hence gain weight. Also, hypersomnia, rather than insomnia, is often a feature.[5]

2.3.2. **Recurrent brief depression** is a form of subsyndromal, or subclinical depression. It is diagnosed in a patient suffering symptoms of major depression, in whom the symptoms are of less than two weeks duration, hence not meeting the diagnostic requirements for major depressive episode. The criteria are not fully established, but despite the short duration of the depressive episodes, there may be significant accompanying disability and a high risk of suicide.[6]

2.3.3. **Post-partum depression** is the most common complication of childbearing, affecting approximately one in eight women after delivery. It must be distinguished from the post-partum 'blues' which affects about half of newly delivered mothers, and is a transient and self-limiting condition. The pattern of symptoms in women suffering from post-partum depression is similar to those in women suffering from episodes unrelated to childbirth. The onset is typically some weeks after childbirth (compared to the blues which occurs within days). Whilst occurring in the post partum period, the aetiology is related both to the stresses of early child rearing as well as more general factors such as other life events and general vulnerability to depression. The maternal illness has the potential to affect the wellbeing and development of the baby. A rarer disorder is postpartum psychosis, which has an earlier onset soon after birth, affects 1-2 women per 1000 births, and is often a manifestation of underlying bipolar disorder.[7]

2.3.4. **Dysthymia** is a form of chronic but subsyndromal or subclinical depression, in which some symptoms of major depression have been present for at least two years, but the number of symptoms has been inadequate to make a diagnosis of major depression. Symptoms typically start at a young age, and patients complain of lethargy, self-doubt, and lack of enjoyment. This condition is extremely prevalent, with one study estimating that dysthymia affects around 3% of the adult population in the US. It more commonly affects women under 65, unmarried persons, and young people with low income. It has been found to have a high comorbidity with other psychiatric disorders.[8] In some cases, a chronic state of dysthymia is punctuated by major depressive episodes. This pattern of illness is referred to as **double depression** and is associated with a high level of psychosocial impairment and high risk of suicide.

2.3.5. **Cyclothymia** is a condition in which there are depressive features, but again, these are inadequate in number and severity for a diagnosis of major depression. These episodes are punctuated by periods of normal mood, and episodes of elevated mood insufficient to meet the criteria for hypomania. Many such patients complain of unpredictable changes in their energy levels, vague physical symptoms and a seasonal pattern to their mood swings.[9]

2.3.6. Whilst the principal features of depression are often easily elicited, some patients

present in a less clear-cut manner. For example they may deny feelings of worthlessness or low self-esteem. Alternatively, they may present with **physical symptoms**, such as pain, or abnormal physical sensations. Others may suffer from **severe psychomotor retardation** and be unable to express what they are experiencing.

2.3.7. **Elderly people** with depression may primarily exhibit disturbance of memory and concentration, and initially appear to be suffering from a form of dementia ('depressive pseudodementia'). Establishing the correct diagnosis in such cases entails a period of clinical observation, including neuropsychological testing, observation for biological features of depression, and in some cases, a trial of antidepressants. In some elderly patients, a depressive episode may co-exist with dementia.

2.3.8. In the **bereaved patient**, differentiating normal grieving from depression can be difficult; the symptoms overlap greatly and the distinction is somewhat arbitrary. The DSM-IV suggests that depression may be diagnosed if symptoms persist for longer than two months after bereavement, or if the patient suffers marked functional impairment, expresses feelings of worthlessness, or has suicidal ideas, psychotic symptoms or psychomotor retardation. The key depressive features of low self-esteem and self-reproach are particularly helpful in identifying the presence of depression. In bereavement, whilst there is a strong sense of loss, there is normally no loss of self-esteem.

3. Aetiology

3.1. The aetiology of depression is complex, and multi-factorial. The current approach is to draw together a number of precipitants into a coherent aetiological schema. Particular emphasis is being placed on interactions between a genetic predisposition to depression, early environmental experiences and psychosocial precipitants.[10]

3.2. The principal areas of research in the aetiology of depression include genetics, biochemical, physiological and neuro-anatomical precipitants, and socio-environmental factors. In addition, there are a number of theories describing personality types and cognitive styles which may predispose to depression. Finally, depression may be related to the presence of other physical and mental disorders.

3.3. **Genetic factors**

3.3.1 Relatives of people suffering from mood disorders are at higher risk of developing a mood disorder themselves. Susceptibility is greatest in first degree relatives of people with mood disorders. For example family studies have indicated that first-degree relatives of patients with depressive disorder have a risk of developing depression themselves of 5.5 – 28.4%. First-degree relatives of people with bipolar disorder have a 5.4 – 14% risk of depression.[11]

3.3.2 The likelihood of twins sharing a mood disorder (concordance) is greater in monozygotic twins than in dizygotic twins. The concordance rate for depressive disorder is around 0.50 in monozygotic twins, and 0.20 in dizygotic twins. Furthermore, the rate in monozygotic twins who are reared apart remains around 0.50, suggesting that the genetic influence is fairly stable, regardless of the psychosocial environment in which the person develops.[11] Adoption studies show that, in people suffering from depression who were adopted in infancy, there is more likely to be a background of depressive illness in their biological family than in the adoptive family. This suggests that genetic factors are more significant than psychosocial influences in the susceptibility to depression.[11] Various genes have been proposed as conferring susceptibility to depression. However, the findings overall are inconclusive. It is most likely that many genes of small effect interact on different biological systems to produce this genetic vulnerability.

3.4. **Biochemical factors**

The function of the brain involves communication between neurones, mediated by a number of neurotransmitter substances. An important class of neurotransmitters is the monoamine group which includes serotonin, dopamine and noradrenaline. A further significant neurotransmitter is acetylcholine. It should be noted that evidence suggesting these substances play a part in depression is conflicting.

3.4.1. **Serotonin** interacts with other mono-amines to regulate core cerebral functions, including appetite, the sleep-wake cycle, cognition and mood. Serotonin deficiency, or changes in the serotonin synaptic pathway including the reuptake transporter and various receptors, have been implicated in depression. There is a range of evidence both in support of and against serotonin as a factor in depression.

3.4.2. Supportive evidence includes studies showing decreased levels of serotonin and its

breakdown products in post-mortem studies of the brain and cerebrospinal fluid of people who suffered from depression.

3.4.3. Further evidence suggestive of a role includes studies of its precursor, tryptophan. The level of tryptophan in the brain and peripheral circulation can be artificially driven to very low levels, resulting in reduced synthesis and release of serotonin. Several studies of patients who underwent this procedure whilst recovering from major depression showed a return of severe depressive symptoms lasting for several hours after tryptophan depletion.[12] In addition medications which enhance serotonergic activity in the brain have an antidepressant effect.

3.4.4. However, there is also evidence against the serotonin theory. Some substances which increase available levels of monoamines, such as amphetamines and cocaine, do not have reliable antidepressant effects. In antidepressants which increase serotonin levels, there is a delay between the enhanced serotonin availability, which is almost immediate, and antidepressant effects, which usually take 1-4 weeks to become apparent. This suggests that increased serotonin is not directly responsible for the improvement in mood. Modern neuroimaging studies have shown varying changes in specific serotonin receptors, and the emerging picture is not yet fully consistent.

3.4.5. Both excessive and inadequate levels of **noradrenaline** have been proposed as having a possible relationship to depression. Underactivity of **dopamine** neurotransmission has been hypothesized as being related to the decreased motivational and activity levels seen in depression. Some studies have shown decreased concentrations of dopamine products in the cerebrospinal fluid of patients with major depression. Excessive activity of **acetylcholine** neurotransmission has been associated with social withdrawal and depression and it is known that some antidepressants reduce levels of available acetylcholine. However, not all medications which reduce levels of acetylcholine have an antidepressant effect.

3.4.6. The research about particular neurotransmitter excesses or deficiencies is complicated by the fact that the transmitter substances and their receptors do not work independently of each other. Cerebral activity results from the simultaneous, convergent action of many neurotransmitters. Thus it is unlikely that abnormalities in the levels of any one particular neurotransmitter can be identified as the principal cause of depression. It is more likely that depression results from disruption to multiple neurotransmitter systems.

3.4.7. A number of other substances have been associated with clinical depression. These include:

3.4.8. **Cortisol**, a steroid hormone, and the mediator of the long term stress response, has been found to be raised in cases of depression, reverting to normal on recovery. Furthermore, Cushing's disease, which involves persistent overproduction of cortisol, includes depressive symptoms in 50-70% of cases. These symptoms resolve when cortisol levels return to normal. In normal biological function, cortisol is secreted in response to acute stress. In the case of depression, however, it is not clear whether the raised cortisol levels are a cause, or a result of the mood disorder, although recent studies suggest that lowering cortisol can be an effective treatment for some patients with depression.

3.4.9. **Thyroid** hormone abnormalities, particularly poor thyroid function, may also be found in depression. These hormones are involved in the regulation of neurotransmitter systems. Thyroid hormone augmentation can be effective in some cases of resistant depression.

3.5. **Neuro-anatomical factors**

3.5.1. **Global cerebral atrophy** is associated with a wide range of psychiatric and medical disorders. Localised brain changes have also been reported in depression. In particular, enlargement of the lateral ventricles has been seen. Magnetic resonance imaging (MRI) has been used to identify changes in the white matter and the peri-ventricular regions of the brain, together with localised changes involving regions that have been identified as important in the control of mood, including the basal ganglia, thalamus, hypothalamus and brainstem. Degenerative changes associated with ageing may contribute to the emergence of depression by causing lesions in these particular areas.

3.5.2. **Functional imaging** of the brain by positron emission tomography (PET) has demonstrated that, in patients with depressive disorder, there is reduced activity in anterior brain structures. Furthermore, injury to the right anterior cortical and subcortical areas, with resulting reduction in activity in these regions, has been found to be associated with depression. It is not yet clear that these changes precede and are responsible for the development of the illness.

3.5.3. **Head injury** has been found to be positively associated with depression. The prevalence of major depression after traumatic brain injury has been estimated at 27% by one multi-centre study, which also found that there was no significant relationship between the severity of the brain injury and the subsequent development of depression. More significant predictors of the likelihood of developing depression after brain injury were psychosocial stressors such as unemployment or poverty at the time of injury.[13]

3.6. **Neuro-physiological factors**

3.6.1. **Sleep abnormalities** are a common feature of depression. In major depressive disorder, specific changes in sleep structure have been identified, including decreased continuity of sleep, more awakenings, early onset of rapid eye movement (REM) sleep, increased duration of REM sleep, and reduced slow-wave sleep. Inadequate slow-wave sleep and reduced sleep efficiency provides an explanation for the subjective fatigue experienced by people with depression who appear to sleep excessively. The abnormalities of sleep structure tend to resolve on recovery from the depressive episode. The extent to which the sleep disorder is a cause or consequence of depression is uncertain. It has generally been assumed that the mood disorder causes the sleep disruption. However, insomnia itself has been consistently shown to be a risk factor for the later development of depression.[14]

3.6.2. **Shift-work** and its relationship to depression has been investigated. One study showed that night-working results in disturbance of concentration, energy, sleep and appetite, and is associated with apathy and increased perception of criticism from others. These features closely mirror those seen in depression.[15] However, this effect is most pronounced in individuals who, prior to night-work, already had depressive symptoms and high levels of sensitivity to interpersonal criticism[16].

3.6.3. **Seasonal depression** has also been linked to abnormal circadian sleep-wake rhythms, although the pathological mechanism is incompletely understood. Neurotransmitter dysfunction has been implicated, particularly with regard to serotonin activity. Light therapy has been shown to be an effective treatment for this form of major depression.[17]

3.7. Socio-environmental factors

3.7.1. Socio-environmental factors associated with depression include the social and occupational environment in which the person lives and works, and the impact of external stressors. Often these factors are studied during or after an episode of depressive illness, making it difficult to draw clear aetiological conclusions about their importance as a precipitant of the illness.

3.7.2. Socio-environmental influences which may impact on a person's risk of depression include parent-child relationships and childhood adversity, family and marital relationships, standard of living, adverse and stressful life events, levels of social support, and specific occupational stressors.

3.7.3. The **parent-child relationship** has a significant impact on mental health in adulthood. Consistent associations have been found between depression and perceived lack of parental warmth, acceptance and affection. Over-critical parents are implicated, particularly those who maintain control through derision, negative evaluation and withdrawal of affection.[18] Childhood sexual abuse is also a strong risk factor for major depression and many other psychiatric disorders.

3.7.4. **Childhood adversity** in general, including loss of a parent or parental separation, family turmoil, and parental mental illness, has a positive association with depression as an adult. This may be due to associated difficulties in making successful role transitions into early adulthood.

3.7.5. **Family relationships**. Studies have consistently found that if a depressed person is treated critically and in an unsupportive fashion by his or her family members, there is less likelihood of recovery, or a greater likelihood of relapse into depression.[19] One study found that, in hospital patients with unipolar depression, the degree to which they perceived their spouse to be critical of them was highly predictive of their risk of relapse after 9 months.[20]

3.7.6. **Marital status** has a gender-dependent effect on the risk of depression. For men, marriage is protective, with separated or divorced men suffering the highest rates of major depression. For women, marriage confers a higher risk of depression.

3.7.7. **Poverty and standard of living** Major depression, along with other common mental disorders, is associated with poor material standard of living, independent of occupational social class.[21] However, *objective* poverty and unemployment have been found to be more strongly associated with an increase in the *duration* of depressive episodes, rather than predictive of the onset of depressive episodes.[22]

3.7.8. There is a consistent association between stressful life events and depression. Particularly significant events include the death of a close relative, assault, serious

marital problems, and divorce/marital breakdown. The more severe the event, the more serious the subsequent episode of depression.[23] However, it is not always appropriate to assume that a particular life event is directly responsible for an episode of depression. Most research in this area relies upon retrospective recall of traumatic events amongst depressed patients, and it is therefore possible that the depression itself introduces bias into the way that events are remembered. Recent research also suggests that being genetically at risk of major depressive disorder is independently associated with an increased risk of experiencing stressful events, suggesting that these individuals select themselves into potentially stressful situations.[24]

3.7.9. **Social support** modifies a person's response to life stressors. Lack of a confiding and intimate relationship leaves an individual vulnerable to depression, while integration in a social network reduces negative outcomes to stressful life events. Social support can be seen as a way of 'buffering' the effects of life events.

3.7.10. **Occupational stress** may be linked to depression. Features of the work environment which have been identified as stressful include organisational problems such as interpersonal conflict and role ambiguity, inappropriate task demands such as excessive or inadequate amounts of work, and a poor physical work environment. It should also be noted that work-related stress may occur simultaneously with external stressors, such as family demands or financial worries, resulting in an accumulation of demands on the individual.

3.7.11. Workplace stressors in studies of military personnel are very much akin to those found in the civilian population. Deployed military personnel however, are also subject to additional stressors including separation from family and friends, and difficulty coping with the physical environment. These factors appear to be more commonly associated with acute psychiatric problems than are stress reactions caused by the trauma of battle. Indeed, a recent study of acute psychiatric casualties from the war in Iraq found that the majority of them were non-combatants[25].

3.7.12. A study of personnel deployed on the KFOR peacekeeping mission in Kosovo identified experiences which were associated with an increased likelihood of developing post-deployment depression. Again, non-combat experiences were found to be particularly stressful. In addition to separation from family, other stressful experiences included witnessing civilian frustration and physical devastation, and knowing that war criminals were often not arrested. Other stressful experiences included fear of having one's unit fired on, patrolling in areas where mines were reported, locating unexploded mines, and seeing human remains.[26]

3.7.13. Some significant predictors of post-deployment depression are unrelated to military service. These included the presence of pre-deployment depressive symptoms, and personal stresses such as family and financial difficulties.

3.7.14. Personality types and cognitive styles

3.7.15. A number of **psychological explanations** have been proposed to explain differences in vulnerability to depressive illness. These identify aspects of personality and thinking style which may predispose to depression. **Cognitive theory** expounds the theory that negative thinking is a cause, rather than a result, of depressive disorders. Depressed patients exhibit several cognitive biases, and are

seen as interpreting setbacks as inevitable, as caused by their own personal failings, and as foreseeing little hope of change from this negative pattern of events. Thus they make little effort to bring about a positive result in response to external stressors, such that further failures ensue. This theory has been backed up by animal experiments which illustrate the phenomenon of 'learned helplessness' – an increasing inability to cope.

3.7.16. Related to the idea of learned helplessness are the **behavioural theories** of depression. These suggest that a deficit of adaptive coping mechanisms for dealing with stress results from a lack of reinforcement of these behaviours. Similarly, it is thought that a person's tendency to exhibit depressive behaviours, such as expressions of personal inadequacy, will be reinforced if they are rewarded by attention and support from others.

3.8. Relationship to other physical and mental disorders

3.8.1. **Secondary Depression** is a term used to describe depression thought to be the result of a co-existing medical, or other psychiatric disorder. Another use of the term is simply to express the simultaneous presence of depression with another illness, without necessarily implying causation. Patients with a severe or chronic physical illness are at significantly increased risk of depression. A number of important physical conditions which predispose to depression are listed in Appendix A. Some medications and substances of abuse are also associated with depression. A number of the more significant medications which have been implicated in depression are listed in Appendix B.

3.8.2. **Other psychiatric conditions** are frequently comorbid with depression. One study found that two thirds of individuals identified as having an episode of major depression also met the criteria for another psychiatric disorder. Most commonly these were anxiety disorders or substance abuse disorder.[27] The presence of anxiety together with depressive disorder makes the depression more refractory to treatment. It is also associated with a higher risk of suicide, possibly due to higher levels of arousal in the depressed patient.

3.8.3. **Schizophrenia** is accompanied by major depressive episode in 25-50% of episodes. In some cases, in which symptoms of depression and psychosis are present in equal measure, a separate diagnosis of **schizo-affective disorder** may be made.

3.8.4. **Personality disorders**, particularly the borderline, antisocial and histrionic forms, are often accompanied by co-existent depression**,** although the majority of patients with depression as a primary disorder do not have a personality disorder.[28] It is not clear how this association develops. It is possible that certain personality traits may predispose to mood disorders. Conversely, a chronic mood disorder may influence the development of pathological personality characteristics. Patients with a co-morbid personality disorder exhibit more severe depressive symptoms and have a poorer prognosis than those without.

3.8.5. **Post-traumatic stress disorder (PTSD)** has been found to have an association with mood disorders, including depression. PTSD can result from any exceptionally stressful or catastrophic experience. Proving the presence of an aetiological link between PTSD and depression depends on demonstrating the temporal relationship

between the two. Clarifying the direction of causality is difficult with many studies reliant on retrospective recall. There is a large overlap in the symptoms of PTSD and major depression.

3.8.6. One large study avoided this pitfall by using a prospective study design to follow the development of psychological symptoms in veterans of the first Gulf War. The results showed a bi-directional relationship between PTSD and depression, but also demonstrated that PTSD more often preceded depression than vice versa. This study also analysed the relationship at a more complex level, by investigating the links between depression and the three principal components of PTSD. The results indicated that symptoms of hyper-arousal and avoidance-numbing more frequently precede depression than vice versa, whereas re-experiencing more often occurred after symptoms of depression had been identified.[29]

3.8.7. **Alcohol abuse** is often associated with depressive disorder, with approximately 50% of patients with depression also exhibiting alcohol misuse or dependency.[30] A study of 6,050 former drinkers, who were abstinent at the time of the study, found that prior alcohol dependence increased the risk of current major depressive disorder more than four-fold. Thus, it would seem there is a relationship between alcohol misuse, or the tendency to develop it, and major depression, even if a person is not currently drinking. The extent of the causal relationship between the two disorders has not so far been established.[31] In patients with both disorders, it has been shown that sustained remission from alcohol misuse significantly increases the chances of remission in depression, and also reduces the likelihood of relapse of depression.[32]

4. Prognosis

4.1. Although major depressive disorder can occur as a single episode, it is likely to recur. The probability of recurrence is particularly high (around 36%) in the first 12 months after recovery from an episode of major depression.[33] One study has shown that the overall risk of recurrence increases by approximately 16% with each new episode of depression.[34]

4.2. Whilst socio-environmental stressors are often clear precipitants of an initial episode, later episodes in those with highly recurrent disorders become more autonomous with stressful events contributing little to the relapse.

4.3. After a first episode of major depression, the overall lifetime risk of a second episode is approximately 50%, and after a third episode the risk of a fourth is about 90%. The period of time between the first and second episodes is usually longer than that between subsequent episodes. Later episodes tend to have an increasingly abrupt onset, and involve more severe symptoms. This progression occurs without regard to the age or gender of the patient.

4.4. Remission from depressive episodes is frequently incomplete. In one study, residual symptoms of major depression were found in 32% of patients 12-15 months after remission. Residual symptoms, such as insomnia, headaches, anxiety and low mood, increase the risk of relapse. One study found that patients with residual symptoms relapsed three times faster than asymptomatic patients.[35] Inadequate treatment is at least partly responsible for residual symptoms, and current treatment strategies emphasize the need to treat patients to full remission of symptoms in order to reduce the risk of relapse and improve the longer term prognosis.

4.5. The duration of a depressive episode is longer in hospitalised patients (who by definition have more severe disease) than those in the community. The median length of an episode of major depression is 5.4 months in hospitalised patients, and approximately 3 months in community patients. In around 10% of patients depression will be chronic, lasting two years or more. The longer major depression has been present, the more likely it is to be persistent. Conversely, it has been found that, in patients who recover, the longer they remain well the less likely they are to develop a subsequent episode of depression. Co-morbidity of alcoholism and personality disorders with depression results in a particularly poor prognosis.

4.6. The mortality rate amongst those suffering from depression is elevated compared with the general population. Suicide is the principal cause of this increased rate, although all-cause mortality excluding suicide is doubled, and recent studies have shown adverse effects of depression on the prognosis of cardiac disease, stroke and diabetes. Compared with rates of death from suicide in the general population, people with major depression have been found to have a 20.35 times higher risk of suicide, and in dysthymia the risk is 12.12 times higher. The risk of suicide is particularly high in double depression.

5. Summary

5.1. Depression is not a single, static disorder, but a dynamic condition. The evolving course of depressive disorder is the result of an incompletely understood interaction between genetics, neurobiology, and socio-environmental experiences.

5.2. In many cases initial episodes occur in response to an external stressor. The degree to which such influences precipitate an episode of depression depends on the intrinsic severity of the stressor, the individual's inherent vulnerability to depression, and their environment.

5.3. Depression may occur as a single lifetime event, but more often the illness pursues a recurrent course. The severity and duration of depressive episodes tends to increase with each new recurrence.

5.4. Depressive illness is associated with impairment in social and occupational functioning, and with an increase in complaints of physical illness. Patients suffering with depression have a poorer outcome in terms of functional ability than people suffering with chronic physical diseases such as diabetes and cardiovascular disease.

5.5. The mortality rate amongst people suffering from depressive disorder is higher than the general population, due to increased rates of suicide and accidental death and to adverse effects on physical health conditions.

6. Related synopses

Personality disorder

Obsessive compulsive disorder

Generalised anxiety state

Alcohol dependence-abuse syndrome

Stress and mental disorder

Stress and physical disorder

Head injury

Chronic fatigue syndrome

Appendix A– Some Medical Conditions associated with Secondary Depression.[36]

Auto-immune Disease	systemic lupus erythematosis, fibromyalgia, rheumatoid arthritis
Cardiovascular	myocardial infarction, angina, coronary artery bypass surgery, cardiomyopathies
Endocrine	hypothyroidism, hyperthyroidism, Cushing's disease, Addison's disease, diabetes mellitus, parathyroid disease
Gastrointestinal	irritable bowel syndrome, chronic pancreatitis, Crohn's disease, cirrhosis, hepatic encephalopathy
Neurological	Parkinson's disease, dementias, Huntington's disease, stroke, traumatic brain injury, multiple sclerosis
Malignancy and Haematological Disease	pancreatic carcinoma, brain tumours
Metabolic	electrolyte disturbances, renal failure, vitamin deficiencies or excess, Wilson's disease, environmental toxins, heavy metal poisoning
Pulmonary	chronic obstructive pulmonary disease, sleep apnoea

Appendix B– Some commonly used drugs which can cause depression

Drug Type	Comments
Acyclovir	At high doses
Alcohol	
Amphetamine-like drugs	
Anabolic steroids	
Anticonvulsants	Usually with high blood levels
Barbiturates	Especially in the elderly
Benzodiazepines	
ß-blockers	
Oral contraceptives	In approximately 15% of users, but mostly with older, higher dose formulations
Corticosteroids	Especially with high doses and withdrawal
Digoxin	Particularly with high blood levels
Disulfiram (Antabuse)	Depression not related to alcohol reactions
Histamine type 2 receptor antagonists	In high doses and in the elderly
Interferon-α	
Isotretinoin	
Levodopa	More commonly in the elderly/with prolonged use
Mefloquine	
Methyldopa	
Metoclopramide	
Metronidazole	
Narcotics	With high doses
Nifedipine	
Non-steroidal anti-inflammatory drugs	Not reported with all drugs in this class
Norfloxacin	
Ofloxacin	
Phenylephrine	Over-use of nasal spray after weeks or months of use.
Thiazide Diuretics	

7. Glossary

adrenals	A pair of hormone-producing organs which lie near to the kidneys.
agitation	Restlessness, a psychomotor expression of emotional tension.
allele	Any one of a series of two or more different genes that occupy the same position on a chromosome.
antisocial personality disorder	A personality disorder that is characterised by antisocial behaviour, with pervasive disregard for and violation of the rights, feelings, and safety of others.
brainstem	The lowest part of the brain, which merges with the spinal cord.
borderline	A personality disorder in which a disordered behaviour pattern emerges by early adulthood, characterised by psychological instability and impulsiveness, often with fear of abandonment and risk of self-harm and suicide.
chronic	Marked by long duration or frequent recurrence over time, and often by slowly progressing severity.
comorbid	Existing simultaneously with and usually independently of another medical condition.
cortical	The surface layer of grey matter of the cerebrum, which functions chiefly to coordinate sensory and motor information.
dizygotic twins	Twins developed from two separate eggs – non-identical twins.
euthymic	Moderation of mood. Not manic or depressed.
histrionic	A personality disorder in which a person, typically immature and self-centred, exhibits behaviour which is intended to gain attention, even though he or she may not be aware of this intent.
hypomania	Resembles mania, but of less intensity.

lateral ventricle	An internal cavity in the cerebral hemispheres.
monozygotic twins	Twins developed from the same egg – identical twins.
neurotransmitter	Substance that transmit nerve impulses.
nihilistic	Delusional belief that oneself, a part of one's body, or the real world does not exist or has been destroyed.
prevalence	The percentage of a population that is affected with a particular disease at a given time.
prospective	A study that starts with the present condition of a population of individuals and follows them into the future.
psychomotor	Motor action directly proceeding from mental activity.
psychotic	Serious mental disorder characterised by defective or lost contact with reality, often with hallucinations or delusions.
retardation	Abnormal slowness of thought or action.
thought broadcasting	The delusion of experiencing one's thoughts, as they occur, as being broadcast from one's head to the external world where other people can hear them.
thought insertion	The delusion that one's thoughts are not really one's own but are being placed into one's mind by an external force.
white matter	Brain tissue composed of myelin-coated nerve cell fibres, which carries information between the nerve cells in the brain and spinal cord.

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