

*Ministry of Defence*

## **Synopsis of Causation**

### **Generalised Anxiety Disorder**

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## **Disclaimer**

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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

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- 1.1. Generalised anxiety disorder (GAD) is a condition characterised by generalised and persistent symptoms of anxiety, resulting from worry. This worry revolves around a number of different issues, for example, family, work, finances, or health and is characteristically out of proportion, pervasive and difficult to control. This may be accompanied by physical symptoms of anxiety, such as abdominal discomfort, hyperventilation, or trembling.
- 1.2. It is important to ensure that symptoms are not related to other psychiatric problems such as an episode of depression, phobic anxiety disorder, panic disorder, or obsessive-compulsive disorder (OCD). A number of medical conditions can also cause patterns of symptoms similar to GAD and these should be excluded before applying the diagnosis of generalised anxiety disorder
- 1.3. Psychiatric disorders are defined in the World Health Organisation's International Classification of Diseases system (ICD-10)<sup>1</sup> and the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-IV).<sup>2</sup> There are quite significant differences between the two classification systems but some researchers describe excellent agreement for the diagnosis of GAD.<sup>3</sup> Other authors are not so confident that the two classification systems measure the same thing.
- 1.4. ICD-10 requires that the sufferer must have primary symptoms of anxiety which are not restricted to any particular environment, and occur nearly every day for at least *several weeks at a time*. Although it requires the presence of autonomic arousal such as increased heart rate, there is a hierarchical structure which means the diagnosis cannot be made if the patient also meets the criteria for panic disorder, phobic disorder, OCD, or hypochondriasis.<sup>1</sup>
- 1.5. DSM-IV puts more emphasis on the presence of 3 out of 6 symptoms such as motor tension, restlessness, and poor concentration that are associated with worry. It requires that the symptoms be of *at least six months duration*.<sup>2</sup>
- 1.6. Both systems do not allow the diagnosis to be made if the criteria for a depressive episode are met, which means if the patient is suffering from clinical depression, then they cannot simultaneously be diagnosed with GAD. However, in clinical practice it may be sometimes necessary to make a diagnosis of depression and GAD. This contributes to the controversy surrounding the validity and specificity of the diagnosis, and can create problems in research. The difficulty in reliably identifying individuals with GAD and high rates of comorbidity has contributed to difficulties in producing good quality research into the condition.
- 1.7. There is a high rate of comorbidity with other psychiatric disorders, especially depression. This observation raises concerns that the disorder is not a separate condition but a prodromal stage of depression, a residual state after an episode of depression, or a severity marker of depression with similar aetiology. However, the research available indicates that the presence of a comorbid disorder does not change the manner of onset, presentation, or course of GAD, suggesting that GAD is indeed an independent disorder and that the diagnostic category is a valid one.<sup>4</sup> It should be noted that comorbidity is common with all anxiety and mood disorders.

- 1.8. There is concern that rather than being a specific illness, GAD is one facet of a so-called “general neurotic syndrome”.<sup>5</sup> It is postulated that an individual might be diagnosed as having GAD, depression, and personality disorder at various points in their life, when actually all these diagnoses are different manifestations of one underlying condition. Some researchers are concerned that focusing on symptom clusters and categorizing them into individual disorders such as GAD detracts from exploration of shared features of emotional disorders that could have greater significance in understanding them.<sup>6</sup> There is concern that meeting exact diagnostic criteria reflects inconsequential variation within a broader syndrome.

## 2. Clinical Features

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- 2.1. **Psychological symptoms** are variable but can include the following:
  - 2.1.1. The individual may suffer from worrying thoughts, fearful anticipation, irritability, sensitivity to noise, restlessness and reduced concentration.
  - 2.1.2. The worry can be “free-floating”, that is, the worrying thoughts may be about anything that comes to mind, or it can relate to certain themes, such as health or financial worries.
  - 2.1.3. GAD is differentiated from other anxiety disorders. In GAD the patient has a number of *worries* about various problems, whereas in phobia the patient has one specific *fear*. In GAD the anxiety is persistent and moderate, while in panic disorder the anxiety is episodic and severe.
- 2.2. **Physical symptoms** vary amongst patients, and may involve a variety of systems:
  - 2.2.1. **Gastrointestinal system.** Symptoms include a dry mouth, difficulty in swallowing, upper abdominal discomfort (such as “butterflies-in-the-stomach”) and loose bowels.
  - 2.2.2. **Respiratory symptoms.** These include shortness of breath and hyperventilation.
  - 2.2.3. **Cardiovascular symptoms.** These include palpitations and chest pain.
  - 2.2.4. **Genitourinary symptoms.** These include altered frequency of urination and amenorrhoea.
  - 2.2.5. **Neuromuscular symptoms.** These may include headache, dizziness, tremor, tinnitus, restlessness, feeling on edge or tense, and an inability to relax.
  - 2.2.6. **Sleep disturbance.** Insomnia and nightmares may be reported.
- 2.3. Within the adult household population of Great Britain in 2000, the prevalence of GAD was 44 adults per 1000, i.e. 4.4%.<sup>7</sup> In this study, GAD was diagnosed where there was symptom duration greater than 6 months, free-floating anxiety, autonomic overactivity, and overall anxiety. This was based on ICD-10. Prevalence in females was slightly higher than in males. Prevalence rates had not changed significantly since a similar previous survey completed in 1993. When compared with adults who had no neurotic disorder, those with GAD were more likely to be aged between 35 and 54 years (55% compared to 35%), and more likely to be divorced or separated (20% compared to 7%). Women with GAD were more likely than women with no neurotic disorder to be living as lone parents (17% compared to 8%). Men with GAD were less likely than those with no neurotic disorder to be single (19% compared to 27%). There was very little difference in educational level, IQ, or social class between those who had GAD and those who did not, but less economic activity in those with GAD.

- 2.4. Using DSM-III-R (an earlier version of DSM-IV) criteria, lifetime prevalence for GAD in the United States was 3.6% for males and 6.6% for females.<sup>8</sup> The criteria for the condition have been met by 5.1% of the population at some time in their lives. Research is inconsistent regarding age of onset but it has been found that GAD is much more common in females, chronic in nature, with episode durations commonly averaging a decade or longer.
- 2.5. **Comorbidity.** The majority (90.4%) of GAD patients have experienced comorbidity with another psychiatric condition: 62.4% major depression, 39.5% dysthymia, 37.6% alcoholism, 35.1% simple phobia, 34.4% social phobia, 27.6% drug abuse, and 23.5% panic disorder.<sup>9,10</sup> Even if the full diagnostic criteria for other diagnoses are not met, 73% of patients with GAD report at least one panic attack,<sup>11</sup> and 73% experience concerns of negative evaluation in social situations.<sup>12</sup>
- 2.6. Epidemiological evidence from different studies is inconsistent. One study found GAD to be twice as common in women, in persons under 30 years old, and in the black population with the lifetime prevalence higher in urban areas and in low-income brackets.<sup>13</sup> However, another study found significant correlations with GAD in persons older than 24 years, people who were separated, divorced or widowed, those who were unemployed, and those who were homemakers.<sup>10</sup>

### 3. Aetiology

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- 3.1. The aetiology of generalised anxiety disorder, in common with most psychiatric conditions, is the outcome of a complex interaction between biological, psychological, and environmental influences on the individual.
- 3.2. There is a lack of aetiological research focusing specifically on GAD. Most aetiological research has been on anxiety disorders in general. However, sections 3.3-3.8 look at factors associated with the diagnosis.
- 3.3. The following two factors may be *non-specific* risk factors, as they are common to many psychiatric disorders. In other words, they may increase the risk of an individual having *any* psychiatric disorder, not just GAD.<sup>14</sup>
  - 3.3.1. **Genetics.** GAD is a disorder that runs in families. If an individual has a first-degree relative who has GAD, then the odds ratio of the person also having the illness is 6.1,<sup>15</sup> which means their risk is about six times that of anyone else who does not have an affected near relative. The exact gene is unknown, but what is inherited may be a general predisposition towards anxiety and depression rather than any specific factor for GAD.<sup>14,16</sup> This could help explain the high rates of comorbidity.
  - 3.3.2. **Parenting.** There is evidence that controlling and overprotective parenting is associated with anxiety disorders. This may encourage avoidant responses in their children, particularly if they have a vulnerable temperament. In turn this may limit the development of adaptive coping strategies.<sup>17</sup> There is a statistical association between parental problems with depression, alcohol, or violence and GAD among American Indians.<sup>18</sup>
- 3.4. **Adverse early experiences.** Parental indifference and physical or sexual abuse was linked to increased rates of GAD, although the study in question looked only at women living in an inner city.<sup>19</sup>
- 3.5. **Personality.** High neuroticism frequently precedes the onset of anxiety disorders. GAD may be strongly related to normally distributed personality traits such as neuroticism, as well as personality disorder traits (avoidant and dependent traits in particular).<sup>20</sup>
- 3.6. **Stress.** In clinical practice, GAD is often seen after stressful events that are perceived as threatening, and can become chronic if the stressful problems persist. Unfortunately, research into the aetiological role of specific events and the subsequent linking of these to a specific diagnosis of GAD has not been undertaken. Very threatening events are said to predict the onset of the condition,<sup>21</sup> and a large survey found that life events led to a greater risk for GAD in men when compared to women.<sup>22</sup> However, this is difficult to assess retrospectively as patients may overestimate the impact of life events in order to explain their symptoms.
- 3.7. **Military service.** A review of a complete cohort of 1,381 Australian veterans of the First Gulf War reported 10 individuals developing GAD after their return.<sup>23</sup> This

represented a 3.3 times increased risk of developing GAD, when compared to a comparison group of 2,924 individuals that were selected randomly from 26,411 Australian Defence Force personnel who were fit to deploy but did not go. During the deployment there were few direct military attacks and no deaths, but there were stressors related to the threat of combat, fear of chemical or biological attack, isolation, and physical discomfort.

- 3.8. **Substance use.** Rates of comorbidity between GAD and substance misuse have been described in section 2.5.
- 3.8.1. **Alcohol.** Alcohol misuse is often comorbid with anxiety disorders,<sup>24</sup> although the nature of the relationship is not always clear. For instance, an individual with co-existent alcohol and anxiety problems may experience anxiety symptoms because they drink heavily; or they may use alcohol to deal with their anxiety symptoms; or their alcohol misuse and anxiety may be entirely coincident; or possibly they possess a trait which predisposes them to both anxiety and alcohol abuse.
- 3.8.2. **Tobacco.** Tobacco smoking is also associated with increased risk of certain anxiety disorders during late adolescence and early adulthood but a causal direction has not been clarified.<sup>25</sup> Smoking may have an effect on chemicals in the brain involved in anxiety regulation.<sup>26</sup>
- 3.8.3. **Cannabis.** A survey of 10,641 adults in Australia found cannabis, alcohol, and tobacco were associated with anxiety or mood disorders. However, once social factors, neuroticism and other drug use were taken into account, the association disappeared for cannabis<sup>27</sup> (although it did remain for the alcohol and tobacco, which is consistent with previous knowledge). In a study of 1,601 teenagers over seven years, the same group of researchers concluded that anxiety and depression were five times more likely in female teenagers who used cannabis, and this held regardless of whether other factors were taken into account.<sup>28</sup>



## 4. Treatment

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- 4.1. The National Institute for Clinical Excellence (NICE) is a UK Government body that reviews data on the efficacy and effectiveness of currently available treatments, before publishing advice about best clinical practice for a variety of medical conditions. It has produced guidance for the treatment of generalised anxiety disorder, summarized in sections 4.2-4.6.<sup>29</sup>
- 4.2. After the condition is recognised, treatment should be offered promptly in a primary care (i.e. General Practice) setting, although referral to specialist services may be necessary.
- 4.3. Treatment can take the form of:
  - 4.3.1. Psychological therapy (cognitive behavioural therapy, or “CBT”)
  - 4.3.2. Pharmacological therapy (the selective serotonin re-uptake inhibitor class of anti-depressants, or “SSRI”)
  - 4.3.3. “Bibliotherapy” which is usually self-help manuals, or computer programs, based on CBT principles
- 4.4. The preference of the person with GAD should be taken into account, although the guideline noted that the evidence suggests that CBT has the longest duration of effect, with the others following in descending order.
- 4.5. CBT aims to help the patient recognise and alter patterns of distorted thinking and dysfunctional behaviour, potentially alleviating the impact of symptoms related to such thinking and behaviour.
- 4.6. Antidepressants, more particularly SSRIs, are the only medication that should be used in the long term. Benzodiazepines should not be used for longer than 2-4 weeks as tolerance and dependence develops.
- 4.7. Research has suggested that such factors as disorder severity, comorbid depression, interpersonal problems, and avoidance of emotions tend to predict treatment failure.<sup>4</sup>

## 5. Prognosis

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### 5.1. Natural history

- 5.1.1. DSM-IV currently excludes episodes of generalised anxiety that last for less than six months. It has been known for some time that episodes of anxiety which last longer than six months have a poor prognosis,<sup>24</sup> and so by its very nature, research based upon DSM-IV criteria paints a bleak prognosis.
- 5.1.2. GAD is a common and long-lasting disorder that leads to significant distress and functional impairment. There is less than 40% remission over 8 years, with most of those who improve doing so in the first 2 years. The majority of patients stay the same.<sup>30</sup>
- 5.1.3. Patients reporting high trait anxiety may suffer from a long-lasting course of GAD and higher levels of comorbidity.<sup>31</sup>
- 5.1.4. The majority of people with GAD, whether comorbid or not, report substantial interference with their lives.<sup>32</sup>

### 5.2. Outcome of treatment

- 5.2.1. The longest follow-up (8-14 years) of psychologically treated individuals shows that 50% of the patients improve significantly, although the other half continued to experience symptoms. Standard ten-session treatment was as effective as longer treatment.<sup>33</sup> Controlled studies have shown these techniques to be useful even in long-standing cases, and for the benefits to be maintained up to 2 years later.<sup>4</sup>
- 5.2.2. Medication can produce long-term benefits but the patient may have to remain on medication for a long period, with a minimum period of at least six months.<sup>29</sup>

### 5.3. Suicide

- 5.3.1. GAD appears to be an independent risk factor for subsequent onset of suicidal ideation and attempts. Moreover, comorbid anxiety disorders may increase the risk of suicide attempts in individuals with mood disorders.<sup>34</sup> A meta-analysis that looked at a range of mental health disorders reported that the suicide rate in those with "anxiety neurosis" was six times higher than the general population, although this was based on only one Swedish study.<sup>35</sup> This was slightly lower than the rate for other anxiety disorders.

## 6. Summary

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- 6.1. Generalised anxiety disorder is a common, disabling condition that tends to have a long-lasting course. Its main feature is persistent uncontrollable worry, with several themes, which results in various anxiety symptoms.
- 6.2. It is a common illness and often co-exists with depression, other anxiety disorders, and personality disorder.
- 6.3. The most significant factors in its aetiology appear to be familial or genetic. Other relevant factors are early adverse experiences, adult exposure to stress, and substance misuse.
- 6.4. The disorder appears to have a poor outcome if left untreated, in that it tends to become long-standing.
- 6.5. There are both psychological and pharmacological therapies that can be beneficial in its treatment.

## **7. Related Synopses**

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Adjustment Disorder

Alcohol Dependence/Alcohol Abuse Syndrome

Bipolar Affective Disorder

Obsessive Compulsive disorder

Depressive Disorder

## 8. Glossary

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amenorrhoea	Abnormal suppression or absence of menstruation.
autonomic disturbances	Disturbances of the autonomic nervous system causing physical symptoms. Examples are racing pulse, hyperventilation, and diarrhoea.
comorbidity	The co-existence in an individual of one disease with another, which may or may not be related.
hyperventilation	Rapid breathing.
meta-analysis	A type of study which analyses the results of many other studies, grouping the results together, so the results have more statistical power.
neuroticism	The general tendency towards negative emotions such as anxiety, worry, and guilt.
neurotic disorders	One of the broad group of psychiatric disorders which includes anxiety disorders, obsessive-compulsive disorder and post-traumatic stress disorder, among others. These conditions may or may not share common origins.
prevalence	The number of individuals in a population who have a certain condition at one point in time.
prodromal	The stage of an illness prior to the full clinical syndrome developing. Symptoms at this stage may be different from those that emerge during the eventual illness.
tinnitus	A sound in one ear or both ears, such as buzzing, ringing, or whistling, occurring without an external stimulus. Usually caused by a specific condition, such as an ear infection, the use of certain drugs, a blocked auditory tube or canal, or a head injury.
worry	To feel uneasy or concerned about something; be troubled.

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