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Generalized anxiety disorder: diagnosis and treatment

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Generalized anxiety disorder (GAD) is relatively common, with lifetime prevalence rates of 4-7%. It is a disorder of chronic uncontrollable worry, compounded by physiological symptoms such as disturbed sleep, muscle tension, and difficulty concentrating. The disorder is associated with seriously impaired social and occupational functioning, comorbidity with other disorders, and increased risk for suicide.[1] GAD can go undiagnosed because of a focus on physical symptoms and because of the stigma of mental illness. However, the disorder can be treated. This article reviews current knowledge about the diagnosis and treatment of GAD, including pharmacotherapy and psychosocial therapies.

SOURCES AND SELECTION CRITERIA

We based this review on articles found by searching PubMed and the Cochrane Database of Systematic Reviews using the terms "generalized anxiety disorder" and "generalised anxiety disorder". Our search was limited to English language articles published between 2005 and 2012. Meta-analyses, reviews, and randomised controlled trials were prioritized.

What is generalized anxiety disorder?

GAD is characterized by excessive worry and symptoms of physiological arousal such as restlessness, insomnia, and muscle tension (box). To meet *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) criteria for the disorder, the patient must have excessive and difficult to control anxiety about several different events or activities.[2] For example, anxiety confined to concern about personal safety would not qualify (but should elicit inquiries about symptoms of post-traumatic stress disorder or agoraphobia, for example). In addition to worry, patients must have at least three of the six physiological arousal symptoms listed in the box. These symptoms must not be caused by another psychiatric or medical disorder, or by the use of drugs, and they must cause serious distress or impairment for the clinical diagnosis to be made. The diagnostic criteria will probably be modified in the new DSM-V (for more information, see www.dsm5.org).

The ICD-10 (international classification of diseases, 10th revision) description of GAD contains slightly different description of symptoms. It focuses on physiological arousal such as trembling, sweating, palpitations, and dizziness and does not require symptoms to be present for six months. It is defined as: "Anxiety that is generalized and persistent but not restricted to, or even strongly predominating in, any particular environmental circumstances (it is "free-floating"). The dominant symptoms are variable but include complaints of persistent nervousness, trembling, muscular tensions, sweating, lightheadedness, palpitations, dizziness, and epigastric discomfort. Fears that the patient or a relative will shortly become ill or have an accident are often expressed." Because most clinical trials use DSM-IV criteria, we will focus on GAD as defined by the DSM-IV classification so that the reader can best evaluate the treatment trial data.

Who gets generalized anxiety disorder?

The lifetime prevalence was determined to be 5.7% in a sample from the United States, a similar rate to that found in other countries.[3] The highest prevalence (7.7%) occurred in the 45-59 year age range, and it was more common in women (7%) than in men (4%). Other predictors in a large epidemiological sample included being separated, widowed, divorced, unemployed, or being a homemaker.[4] In a study of children followed into adulthood, low socioeconomic status, childhood maltreatment, internalizing problems, and conduct problems in childhood were risk factors.[5] It is also associated with serious disability and impaired quality of life. In an international study of disability caused by mental illness, 38% of people with GAD had moderate to severe occupational role impairment, with

DSM-IV diagnostic criteria for generalized anxiety disorder

Excessive anxiety and worry occurring more days than not for at least six months
Worry that is difficult to control
The anxiety or worry is associated with three or more of the following:
- Restlessness or feeling "keyed up" or on edge
- Being easily fatigued
- Difficulty concentrating or mind going blank
- Irritability
- Muscle tension
- Sleep disturbance

The focus of the anxiety is not part of another disorder (such as fears of embarrassment in public in social anxiety disorder)

SUMMARY POINTS

Generalized anxiety disorder (GAD) is associated with substantial distress and disability

GAD is often associated with other medical and psychiatric disorders

Antidepressants, such as sertraline, are generally first line medical treatment options

Psychotherapy and other psychosocial treatments can also be effective

GAD increases the risk of major depression, so preventive approaches should be put in place

an average of 6.3 days a month of missed work or loss of role functioning.[6]

How is generalized anxiety disorder diagnosed?

The disorder is not well recognized in primary care. In a large study of patients and their primary care physicians, physicians correctly recognized and diagnosed GAD only 34% of the time.[7] Part of the problem may be the misdiagnosis of anxiety as depression. In one primary care study, only 23% of the patients with pure anxiety were diagnosed with anxiety, compared with 65% of those with pure depression.[8] In other work, researchers examined patients who had been given a false positive diagnosis of depression: 27% of these patients had had an anxiety disorder instead.[9]

In addition, a focus on somatic symptoms may distract patients and doctors from the psychological symptoms; it is known that patients with GAD seek help from primary care more often than the general population. For example, a study of healthcare utilization patterns found that such patients visited primary care an average of 5.6 more times a year than age and sex matched controls without anxiety or depression.[10] Patients presenting with GAD also have higher rates of medical conditions. Associations have been found between GAD and increased rates of pain and gastrointestinal, cardiovascular, endocrine, and respiratory conditions.[11 12] Dysfunctional neural processing of emotional stimuli is thought to be involved in the pathophysiology of the disorder, but this area is poorly understood and research has been minimal.[13 14]

To improve detection and treatment, the International Consensus Group on Depression produced a consensus statement on GAD, which recommends two screening questions: "During the past four weeks, have you been bothered by feeling worried, tense, or anxious most of the time?" and "Are you frequently tense, irritable, and having trouble sleeping?"[15] However, it is not known how sensitive or specific these questions are.

Does generalized anxiety disorder occur with other disorders?

Psychiatric comorbidity is common in GAD—29-62% of patients are estimated to have major depression.[4 7] Other common comorbidities are social anxiety disorder (34%) and alcohol misuse (38%). Unfortunately, patients who also have comorbid psychiatric disorders are more impaired and have a less successful response to treatment than those with GAD alone.[16] The high comorbidity (and symptom overlap) with depression has contributed to the uncertainty about whether GAD is distinct from depression. However, symptoms unique to GAD—such as worry, differential response to benzodiazepines (not effective for depression), different patterns of REM sleep disturbance, and opposing patterns of response to emotional stimuli in the laboratory (relative insensitivity in depression and hyperactivity in GAD)—support it being a distinct disorder.[17 18] When making a diagnosis in a patient with current depression, symptoms that overlap with depression—such as restlessness, difficulty concentrating, and sleep disturbance—cannot be used in the diagnosis of GAD. Ultimately, however, distinguishing between GAD and GAD with comorbidities should not overly concern the clinician because many treatment strategies are the same.

Although they may be distinct disorders, the presence of GAD predisposes to the subsequent development of major depression. One large prospective study of adolescents and adults found that GAD increased the odds of developing depression within four years 4.5-fold (odds ratio 4.5, 95% confidence interval 1.9 to 10.3).[19] Interestingly, drug treatment for GAD significantly lowers the risk of developing major depression.[20]

What is known about the causes?

Both genetic and environmental factors play a role in the development of GAD. In 2001, a meta-analysis of data from family and twin studies of several anxiety disorders found that GAD has a modest heritability (0.32, compared with 0.43 for panic disorder).[21] More recently, a case-control association study of 1059 Spanish primary care attendees found that a polymorphic variation at the serotonin 1-A receptor gene was associated with the common clinical presentation of comorbid major depression and GAD.[22] The above meta-analysis also found that environmental experiences are significantly associated with GAD, highlighting the importance of environmental stressors as a risk factor.

What are the treatment options?

Treatment options include psychological therapies and drugs. Psychological therapies include cognitive behavioral therapy (CBT), behavioral therapy, relaxation response training, and mindfulness meditation training. Of these, CBT is the most well studied and commonly used. Drugs include antidepressants, notably the serotonin reuptake inhibitors as first line agents, benzodiazepines, and the anticonvulsant pregabalin. National Institute for Health and Clinical Excellence (NICE) guidelines recommend treating patients with active substance dependence (different from non-harmful substance misuse) before starting treatment. Unfortunately, it is unclear whether psychotherapy or drugs should be tried first, with some studies showing a benefit of CBT over drugs,[23] and others showing a benefit of drugs, such as sertraline, over CBT.[24] The decision should be made after a discussion with the patient, during which the patient's values, attitudes, beliefs, preferences, and resources are reviewed. Furthermore, it is unclear whether the combination of drugs and psychotherapy is better than using one strategy alone.

What psychosocial treatments can be used?

Several types of psychotherapy have been used, with varying levels of empirical support. For anxiety disorders, CBT—a time limited symptom focused treatment—is the most well studied and highly utilized. Several well conducted meta-analyses have shown significant benefit of CBT compared with control groups,[25-27] and NICE guidelines recommend CBT as first line treatment.

This technique traditionally combines cognitive therapy—which focuses on monitoring thoughts and understanding self perpetuated cognitive distortions, habitual thought patterns, and subsequent behaviors—with behavioral therapy, which aims to expose the patient to feared experiences (originally, phobias). In GAD, targeted cognitions might, for example, be negative interpretations of neutral events that can be systematically evaluated and questioned. People with the disorder are more likely to see ambiguous or neutral stimuli as potentially threatening than those without an anxiety disorder,[28 29] so automatic anxious thought patterns can

be reduced by evaluating thoughts and impressions more objectively. Behavioral therapy is more difficult in GAD than with simple phobias, because worry based anxiety triggers for GAD are more difficult to target, more diffuse, and often shift. One approach has been to use exposure techniques to focus attention on the worries, which themselves may be serving as avoidance against more distressing emotions, such as anger or grief.[30 31]

CBT is usually provided by a specially trained psychotherapist on an individual basis, with six to 12 sessions of one hour's duration as standard. Some studies suggest that CBT can be delivered over the internet, but how it compares to office based CBT is unclear. There is also preliminary evidence that internet based CBT administered by a non-clinician may be effective, although only one randomized controlled trial has been published to date and it was not tested against standard CBT.[32]

Several other psychotherapeutic approaches can be combined with CBT. For example, relaxation response training, in the form of progressive muscle relaxation or diaphragmatic breathing, has been added to CBT or used alone. Two small to medium sized randomized controlled studies comparing cognitive therapy alone with relaxation training alone found that they both significantly and equally reduce anxiety symptoms in GAD.[33 34] Meta-cognitive therapy uses similar techniques to those of cognitive therapy (working to correct automatic or distorted thinking) but also tackles the worry about worrying itself—for example, thoughts that the worrying will become uncontrollable or will cause negative consequences for the patient. The therapy focuses instead on changing beliefs about worry and guides patients away from a focus on attempts to control the worry.[35]

Two newer psychotherapies have recently been introduced for the treatment of GAD; both share a theoretical framework with CBT but include mindfulness training. Mindfulness was originally introduced in mental health treatment settings through meditation training strategies, such as mindfulness based stress reduction.[w1] Mindfulness teaches participants to increase awareness of present moment experiences, such as thoughts and emotions, without judgment or striving to make the experience last or disappear. One of these newer psychotherapies, which has support from a small but well conducted randomized controlled trial, is acceptance-based behavioral therapy. This therapy focuses on accepting problems rather than striving for immediate change, and uses mindfulness to help patients foster a compassionate and non-judgmental awareness of their experiences (which promotes clearer decision making) and a focus on present moment experiences rather than worries.[w2] Emotion regulation therapy also uses mindfulness training but focuses on addressing deficits in regulating emotions through additional techniques.[w3] The use of mindfulness meditation training for GAD is validated by a recent small randomized controlled trial, which found significant benefits compared with an active control class.[w4]

Traditional psychodynamic psychotherapy has been less well studied in GAD, possibly because of methodological challenges in studying a longer and less directed treatment in which the focus varies greatly among individuals. However, in one randomized controlled study from the United Kingdom, which measured the effect of analytically based psychotherapy for GAD, after just six months 42% of patients had "moderate" to "very considerable" improvements in symptoms.[w5] More recently, short term psychodynamic psychotherapy was compared with CBT in a group of 57 patients with GAD as part of a randomized controlled trial.[w6] Both treatments showed significant decreases in anxiety symptoms with no difference between the treatments in the primary outcome measure.

Although not a treatment for GAD by itself, education on sleep hygiene can be useful in primary care given the high frequency of sleep disturbance in this disorder. It is sometimes used with CBT to ensure the best possible sleep efficiency and quality. Advice includes going to bed and waking up at the same time each day, eliminating alcohol after 6 pm, and getting out of bed if unable to fall asleep, to avoid negative associations with the bed environment.[w7] In addition, although not widely studied in GAD, physical exercise decreased anxiety symptoms in at least one small randomised controlled trial.[w8] Lastly, self help books or manuals may be useful, according to a meta-analysis of six randomized controlled trials, two of which showed a benefit over a waiting list control.[w9-w11]

When should drugs be prescribed?

In 2011, NICE issued treatment guidelines outlining an algorithm for the treatment of GAD. It recommended drug treatment if symptoms cause marked functional impairment. This was defined as self reported difficulty in functioning in the domains of work or school, social or leisure, and family life; higher scores on screening instruments such as the seven item "GAD-7"[w12]; or persistence of symptoms despite psychoeducation and low intensity psychological intervention (such as self help and psychoeducational groups). Currently, there is no clear time frame for exactly when drugs should be considered. One large open label study examining the duration of "untreated" GAD (no drug treatment) found that treatment (antidepressants) was more successful when started within one year, suggesting that drugs should be offered within one year of persistent symptoms.[w13] This treatment effect was not found with benzodiazepines.

Which drugs are effective?

Antidepressants

Antidepressants have well documented efficacy in the treatment of GAD, regardless of the presence of comorbid depression.[w14] Treatment efficacy is measured by clinical response (defined in most studies as >50% reduction in HAM-A (Hamilton anxiety rating scale) score from baseline) or remission (defined as the proportion of patients with a final HAM-A score of ≤7). Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine (noradrenaline) reuptake inhibitors (SNRIs) are considered first line treatment options, largely because of their combined efficacy, tolerability, and safety profile. Response and remission rates vary across studies. A 2012 literature review of 50 studies attempted to clarify the expected clinical response and remission rates for GAD treated by drugs. The authors reported that the probability of a response with first line therapy is 67.7%, compared with 54.5% for second line therapy.[w15] Remission rates for first line therapy averaged 39.7%, but insufficient data were available in the reviewed

studies on remission for second line therapy. "Second line therapy" in this study was diverse, including benzodiazepines, buspirone, and pregabalin, which limited the predictive value for this arm of the treatment. One review suggests that, although it is difficult to predict reliably which patients will respond to treatment, response to antidepressants is less likely if there is no evidence of an effect within four weeks.[w16] Others have suggested that a minimum trial period should be eight weeks or more, because 44% of patients with another anxiety disorder who did not respond to an SSRI at four weeks responded by 12 weeks.[w9 w11]

The SSRI, sertraline, is recommended by NICE as the initial treatment for GAD. This recommendation is based on its cost effectiveness (it is available as a generic). We are unaware of any head to head trial demonstrating an efficacy advantage for sertraline over other SSRIs or SNRIs for GAD. However, known clinical advantages of sertraline include its minimal drug-drug interactions (making it preferable to fluoxetine, paroxetine, and fluvoxamine), the lack of associated electrocardiographic changes (compared with citalopram), and its lower risk of symptoms on discontinuation compared with paroxetine and venlafaxine.

If no effect is seen after a four to eight week trial of an SSRI, consider switching to another SSRI or to the SNRI class of antidepressants. However, if a partial effect at is seen at four weeks, it is worth waiting until eight weeks because the effect of SSRIs can continue to increase during this period. The SNRIs, venlafaxine and duloxetine, can also be considered first line treatment options for GAD. Both are licensed in the UK for this indication. Their efficacy has been shown in several randomized placebo controlled studies of adult outpatients with GAD.[w17-w23] A large 24 week double blind placebo controlled study of venlafaxine for GAD in primary care patients with and without depression found a significant reduction in HAM-A score for depressed and non-depressed venlafaxine treated groups (a net decrease of 2.1 points) compared with placebo.[w22] Another large double blind placebo controlled study examined the efficacy and tolerability of duloxetine for the treatment of patients with GAD and found that duloxetine (at 60 mg/day and 120 mg/day) was efficacious, as measured by a significantly greater reduction in HAM-A score compared with placebo. Patients treated with duloxetine also had greater functional improvements as measured by scores on the Sheehan disability scale.[w17]

Other drugs

Pregabalin is an anticonvulsant and antineuralgic agent commonly prescribed for diabetic peripheral neuropathy and postherpetic neuralgia. Since 2000, several randomized placebo controlled studies have examined the efficacy of pregabalin for the treatment of GAD.[w24-w29] NICE guidance suggests that pregabalin be offered as an initial treatment option for patients with GAD who cannot tolerate SSRIs or SNRIs. Similar to benzodiazepines, pregabalin has a rapid onset of action, with anxiolysis occurring within one week of starting treatment. Sedation, dizziness, headache, and dry mouth are the most common side effects.[w30] Although pregabalin is generally not considered habit forming, there have been case reports of misuse and symptoms on withdrawal. Sudden discontinuation of pregabalin and other anticonvulsants has been associated with an acute confusional state, with reversible vasogenic edema of the splenium of the corpus callosum.[w31 w32] Gabapentin, another anticonvulsant drug often used for neuropathic pain, has also been used off label for the treatment of GAD, although evidence favors its use only for social anxiety.[w33]

Benzodiazepines have confirmed efficacy primarily for the short term treatment of GAD.[w34] Because of their habit forming potential and the availability of alternative non-habit forming drugs, NICE guidance recommends that they are offered for the treatment of GAD only as a short term measure in crises. Moreover, unwanted side effects (including sedation and psychomotor impairment) and the potential for withdrawal symptoms (necessitating a gradual discontinuation of treatment) limit their suitability. Short acting benzodiazepines such as alprazolam may lead to rebound anxiety, which can inadvertently promote long term use. Benzodiazepines (ideally longer acting ones like clonazepam) are mainly recommended as short term (≤1 month) treatment for acute anxiety. They can also be used as an initial adjunct to antidepressants given the delayed onset of action of these drugs and the ability of benzodiazepines to attenuate some of the initial side effects of SSRIs and SNRIs.[w35 w36]

Buspirone is a non-benzodiazepine anxiolytic that is effective in the treatment of GAD.[w37] A large well conducted placebo controlled trial of buspirone for the treatment of GAD with mild depressive symptoms showed a significant reduction in HAM-A scores compared with placebo.[w37] The efficacy of buspirone compared with antidepressants or pregabalin is unclear, given the current lack of head to head trials. Comparison studies of buspirone versus benzodiazepines have mixed results, although buspirone may be less effective in patients recently treated with benzodiazepines.[w38] The advantage of this drug over benzodiazepines is its lack of sedation, withdrawal symptoms, and physical or psychological dependence. Two to four weeks or longer are typically needed for a response.

Placebo has been used as the main comparator in most studies, and few head to head clinical studies exist. Thus, little is known about the comparable efficacy of the drugs used to treat GAD. A recent systematic review that pooled data from 27 randomized controlled trials of various drugs found a possible response and remission advantage for fluoxetine compared with all other treatments tested (benzodiazepines, buspirone, and quetiapine were not included).[w16] More head to head studies are needed. Augmentation pharmacotherapy for GAD is another area that requires further study.

Unlicensed treatments used in refractory GAD

If patients do not improve despite the use of treatments of adequate duration, consider unlicensed treatments as a possible next step. Unlicensed treatments should be initiated only by a specialist.

Recently there has been increased interest in the efficacy of second generation antipsychotics, both as monotherapy and as an augmentation strategy,[w39-w41] because only a minority of patients with GAD achieve remission despite current treatments. A recent systematic review and meta-analysis looked at augmentation with second generation antipsychotics and monotherapy in the treatment of GAD.[w42] The study reviewed five separate randomized placebo controlled augmentation studies (total

TIPS FOR NON-SPECIALISTS

Generalized anxiety disorder (GAD) is prevalent in primary care settings
GAD is more than just a tendency to worry and should not be ignored
There must be more than one topic of worry and the disorder must last for at least six months
Onset after age 35 years, lack of history, and lack of stressors suggest a physical cause
Consider GAD when patients present with unexplained somatic problems
Recommend avoidance of nicotine and excess caffeine and alcohol
Recommend exercise to help sleep and relieve tension
Review the use of over the counter drugs regularly
Individualize treatment on the basis of severity, arousal, somatization, comorbidities, and acceptability to the patient
Discuss psychosocial and drug treatments with patients
Antidepressants may take four weeks to take effect

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

Anxiety and Depression Association of America (www.adaa.org/)—Provides research updates and free educational podcasts

National Institute for Health and Clinical Excellence. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults: management in primary, secondary and community care. 2007. http://publications.nice.org.uk/generalised-anxiety-disorder-and-panic-disorder-with-or-without-agoraphobia-in-adults-cg113

Resources for patients

Anxiety and Depression Association of America (www.adaa.org/)—Educational resources about diagnosis and treatment, including real patient stories; registration not required

Brain and Behavior Research Foundation (http://bbrfoundation.org/anxiety)—Resources and information about anxiety disorders and other comorbid disorders; includes recovery stories from patients with mental illness

NHS Choices (www.nhs.uk/conditions/anxiety/pages/introduction.aspx)—UK website that describes the disorder along with its treatment and self help tips

of 912 patients), which failed to show a significant clinical advantage for second generation antipsychotics over placebo. Moreover, augmentation was associated with a higher dropout rate because of adverse effects. The same review found more promising results with studies of second generation antipsychotic monotherapy. Four randomized placebo controlled monotherapy studies (total of 1383 patients) showed significant efficacy of quetiapine monotherapy (up to 150 mg/day) over placebo. As with the augmentation studies, patients treated with quetiapine had an increased risk of all cause discontinuation and weight gain.[w42] Currently, antipsychotics should not be offered as an initial treatment option for GAD.[w43]

How long should drugs be continued?

If a particular drug is effective, the optimal treatment duration is generally one year,[w43] given the lower relapse rate for patients who continue on pharmacotherapy versus placebo.[w44] Treatment should also be continued for several months because a longer course of treatment increases the likelihood of remission.[w44 w45] This observation is supported by two double blind placebo controlled trials of extended release venlafaxine, which found higher response and remission rates when the initial eight week treatment course was extended to six months.[w46]

When should I refer?

GAD is more than just excessive worrying, and it is often a chronic disorder. In a group of older people with GAD who still remained symptomatic, the mean duration of the illness was 37 years.[w47] However, when successfully treated, the disorder can remit. A study that followed GAD patients, most of whom received treatment, over 22 years found that 63% had been symptom free for at least one year at the time of follow-up.[w48] This is similar to another study that found 58% recovery over 12 years. The course of GAD was longer in those with comorbid depression or substance use disorders.[w49]

Healthcare professionals should consider how long the worries have been present, whether they span several different topics of concern, and whether they are associated with the physical symptoms listed above. Physical examinations and laboratory testing can help rule out medical causes of anxiety or the physical symptoms associated with GAD. The possibility of thyroid dysfunction, hypoglycemia, hyperparathyroidism, arrhythmias, chronic obstructive pulmonary disease, seizure disorder, and more rarely pheochromocytoma should be investigated.

Investigate effects related to sympathomimetics, β adrenergic agonists, corticosteroids, thyroid hormone, and other drugs along with possible effects of substance use (such as caffeine, amphetamines, cocaine) and withdrawal (such as alcohol, sedative hypnotics). When no associated with other disorders, GAD can often be treated successfully in primary care with the first line drugs listed above or with referral to psychotherapy. Primary care providers can also successfully advise patients with sleep difficulties on sleep hygiene and teach some of the simple CBT skills.[w9] However, in the presence of comorbid depression, alcohol or substance misuse, or another anxiety disorder, referral to a psychiatrist may be indicated.

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ANSWERS TO ENDGAMES, p 48

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PICTURE QUIZ

The management of open tibial shaft fractures

1 Open fracture of the tibia, Gustilo-Anderson type 3b.
2 According to the advanced trauma life support protocol as well as joint guidelines on the management of open fractures of the lower limb from the British Association of Plastic Reconstructive and Aesthetic Surgeons (BAPRAS) and British Orthopaedic Association (BOA). The patient requires systematic repeated neurovascular assessment, intravenous antibiotics, tetanus vaccination, reduction and stabilisation of the fracture, and referral to orthopaedics and plastic surgery.
3 Early debridement, skeletal stabilisation, and soft tissue reconstruction with antibiotic cover until soft tissue closure or 72 hours after the injury occurred.
4 If the patient is in a specialist unit, on the next scheduled joint orthoplastic surgery list unless there is severe contamination. If in a non-specialist unit, primary debridement with or without fracture fixation should be carried out on the next scheduled orthopaedic list in discussion with the local plastic surgery unit.
5 Neurovascular compromise, compartment syndrome, infection, delayed union, non-union, and limb loss.

ANATOMY QUIZ

Magnetic resonance imaging of the sagittal structures in the brain

A: Basilar artery
B: Optic nerve
C: Cingulate gyrus
D: Pons
E: Fourth ventricle

STATISTICAL QUESTION

Confounding in clinical trials

Statements *a*, *b*, *c*, and *d* are all true.

CASE REPORT

Multiple enlarging nodules on the lower limb

1 Squamous cell carcinoma (SCC). Given her history of SCC, these lesions are highly suspicious of a recurrence.
2 Examination of the draining lymph node basins (popliteal and inguinal lymph nodes in this patient) is essential to identify possible lymph node involvement. A full skin examination should also be performed to exclude concurrent skin cancers.
3 A histological diagnosis is of paramount importance, so a punch biopsy or incisional biopsy of the lesion is the first line investigation. Palpable lymph nodes can also be biopsied, and staging computed tomography should be organised if there is evidence of other systemic spread, such as lymphadenopathy or weight loss.
4 Within the United Kingdom, all patients with a histological diagnosis of SCC should be discussed at a skin cancer multidisciplinary team meeting. Surgical excision, which is normally carried out by plastic surgeons or dermatologists, is the gold standard. The aim of treatment is complete excision with 4 mm margins at least. Patients are followed up for two to five years, depending on the risk of recurrence.