
ANXIETY AND MEDICATION

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Anxiety is an emotion characterized by an unpleasant state of inner turmoil, often accompanied by nervous behavior, such as pacing back and forth, somatic complaints, and rumination. It is the subjectively unpleasant feelings of dread over anticipated events, such as the feeling of imminent death. However, with psychotherapy or a combination of psychotherapy and medication anxiety disorders have become highly treatable. Since there is a high comorbidity with other conditions, such as depression and obsessive-compulsive disorder (OCD), the use of an antidepressant for both the anxiety and depression can lead to significant improvements in the patient's quality of life. This article explores the biology of anxiety and the different types of medication to treat it.

Keywords: anxiety, generalized anxiety disorder, panic attacks, medication, psychiatry

Table of Contents

Introduction.....	3
Anxiety vs Fear	3
Diversity of Anxiety	3
Duration	3
Psychotherapy and long-term medication.....	4
Risk Factors for Anxiety	4
Neuroanatomy	4
Genetic	4
Medical conditions	5
Substance-induced	5
Psychological	5
Evolutionary psychology	6
Social	6
Medication	6
Short-term, standby medication	7
Benzodiazepines.....	7
Long-term medication.....	7
Selective Serotonin Reuptake Inhibitors (SSRIs)	7
Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)	8
Non-benzodiazepine anxiolytics (5-HT _{1A} autoreceptor agonists)	8
GABA analogues and other mechanisms	8
Conclusion	9
References.....	10

Introduction

Anxiety is an emotion characterized by an unpleasant state of inner turmoil, often accompanied by nervous behavior, such as pacing back and forth, somatic complaints, and rumination. [1] It is the subjectively unpleasant feelings of dread over anticipated events, such as the feeling of imminent death. [2]

Anxiety has biological causes, but it is often also a sign that something in life is 'out of sync'. (Haverkamp, 2018b) A combination of psychotherapy and medication is therefore often the optimal treatment. In less severe cases, psychotherapy alone can also be sufficient.

Anxiety vs Fear

Anxiety is not the same as fear, which is a response to a real or perceived immediate threat, [3] whereas anxiety is the expectation of future threat. [3] Anxiety is a feeling of uneasiness and worry, usually generalized and unfocused as an overreaction to a situation that is only subjectively seen as menacing. [4] It is often accompanied by muscular tension, [3] restlessness, fatigue and problems in concentration. Anxiety can be appropriate, but when experienced regularly the individual may suffer from an anxiety disorder. [3]

Diversity of Anxiety

People facing anxiety may withdraw from situations which have provoked anxiety in the past. [5] There are various types of anxiety. Existential anxiety can occur when a person faces angst, an existential crisis, or nihilistic feelings. People can also face mathematical anxiety, somatic anxiety, stage fright, or test anxiety. Social anxiety and stranger anxiety are caused when people are apprehensive around strangers or other people in general. Furthermore, anxiety has been linked with physical symptoms such as IBS and can heighten other mental health illnesses such as OCD and panic disorder. The first step in the management of a person with anxiety symptoms is to evaluate the possible presence of an underlying medical cause, whose recognition is essential in order to decide its correct treatment. [6][7] Anxiety symptoms may be masking an organic disease, or appear associated or as a result of a medical disorder. [6][7][8][9]

Duration

Anxiety can be either a short term "state" or a long term "trait". Whereas trait anxiety represents worrying about future events, anxiety disorders are a group of mental disorders characterized by feelings of anxiety and fear. [10] Anxiety disorders are partly genetic but may also be due to drug use, including alcohol, caffeine, and benzodiazepines (which are often prescribed to treat anxiety), as well as withdrawal from drugs of abuse. They often occur with other mental disorders, particularly bipolar disorder, eating disorders,

major depressive disorder, or certain personality disorders. Common treatment options include lifestyle changes, medication, and therapy.

Psychotherapy and long-term medication

In general medicine, there is still a reflex to prescribe only short-term medication for symptoms of anxiety and panic attacks. While anxiolytics have their place in the treatment of anxiety and panic attacks, especially in reducing the patient's anxiety about having anxiety or panic attacks in the future, they should be an add-on to a combination of psychotherapy and long-term medication, such as an antidepressant from the group of selective serotonin reuptake inhibitors (SSRIs).

Risk Factors for Anxiety

Neuroanatomy

Neural circuitry involving the amygdala (which regulates emotions like anxiety and fear, stimulating the HPA Axis and sympathetic nervous system) and hippocampus (which is implicated in emotional memory along with the amygdala) is thought to underlie anxiety. People who have anxiety tend to show high activity in response to emotional stimuli in the amygdala. Some writers believe that excessive anxiety can lead to an overpotentiation of the limbic system (which includes the amygdala and nucleus accumbens), giving increased future anxiety, but this does not appear to have been proven.

Research upon adolescents who as infants had been highly apprehensive, vigilant, and fearful finds that their nucleus accumbens is more sensitive than that in other people when deciding to make an action that determined whether they received a reward. This suggests a link between circuits responsible for fear and also reward in anxious people. As researchers note, "a sense of 'responsibility', or self agency, in a context of uncertainty (probabilistic outcomes) drives the neural system underlying appetitive motivation (i.e., nucleus accumbens) more strongly in temperamentally inhibited than noninhibited adolescents".

Genetic

Genetics and family history (e.g., parental anxiety) may predispose an individual for an increased risk of an anxiety disorder, but generally external stimuli will trigger its onset or exacerbation. Genetic differences account for about 43% of variance in panic disorder and 28% in generalized anxiety disorder. Although single genes are neither necessary nor sufficient for anxiety by themselves, several gene polymorphisms have been found to correlate with anxiety: PLXNA2, SERT, CRH, COMT and BDNF. Several of these genes influence neurotransmitters (such as serotonin and norepinephrine) and hormones (such as cortisol) which are implicated in anxiety. The epigenetic signature of at least one of these genes BDNF has also been associated with anxiety and specific patterns of neural activity.

Medical conditions

Many medical conditions can cause anxiety. This includes conditions that affect the ability to breathe, like COPD and asthma, and the difficulty in breathing that often occurs near death. Conditions that cause abdominal pain or chest pain can cause anxiety and may in some cases be a somatization of anxiety; the same is true for some sexual dysfunctions. Conditions that affect the face or the skin can cause social anxiety especially among adolescents, and developmental disabilities often lead to social anxiety for children as well. Life-threatening conditions like cancer also cause anxiety.

Furthermore, certain organic diseases may present with anxiety or symptoms that mimic anxiety. These disorders include certain endocrine diseases (hypo- and hyperthyroidism, hyperprolactinemia), metabolic disorders (diabetes), deficiency states (low levels of vitamin D, B2, B12, folic acid), gastrointestinal diseases (celiac disease, non-celiac gluten sensitivity, inflammatory bowel disease), heart diseases, blood diseases (anemia), cerebral vascular accidents (transient ischemic attack, stroke), and brain degenerative diseases (Parkinson's disease, dementia, multiple sclerosis, Huntington's disease), among others.

Substance-induced

Several drugs can cause or worsen anxiety, whether in intoxication, withdrawal, or from chronic use. These include alcohol, tobacco, cannabis, sedatives (including prescription benzodiazepines), opioids (including prescription pain killers and illicit drugs like heroin), stimulants (such as caffeine, cocaine and amphetamines), hallucinogens, and inhalants. While many often report self-medicating anxiety with these substances, improvements in anxiety from drugs are usually short-lived (with worsening of anxiety in the long-term, sometimes with acute anxiety as soon as the drug effects wear off) and tend to be exaggerated. Acute exposure to toxic levels of benzene may cause euphoria, anxiety, and irritability lasting up to 2 weeks after the exposure.

Psychological

Poor coping skills (e.g., rigidity/inflexible problem solving, denial, avoidance, impulsivity, extreme self-expectation, affective instability, and inability to focus on problems) are associated with anxiety. Anxiety is also linked and perpetuated by the person's own pessimistic outcome expectancy and how they cope with feedback negativity. Temperament (e.g., neuroticism) and attitudes (e.g. pessimism) have been found to be risk factors for anxiety.

Cognitive distortions such as overgeneralizing, catastrophizing, mind reading, emotional reasoning, binocular trick, and mental filter can result in anxiety. For example, an overgeneralized belief that something bad "always" happens may lead someone to have excessive fears of even minimally risky situations and to avoid benign social situations due to anticipatory anxiety of embarrassment. Such unhealthy thoughts can be targets for successful treatment with cognitive therapy.

Psychodynamic theory posits that anxiety is often the result of opposing unconscious wishes or fears that manifest via maladaptive defense mechanisms (such as suppression, repression, anticipation, regression, somatization, passive aggression, dissociation) that develop to adapt to problems with early objects (e.g., caregivers) and empathic failures in childhood. For example, persistent parental discouragement of anger may result in repression/suppression of angry feelings which manifests as gastrointestinal distress

(somatization) when provoked by another while the anger remains unconscious and outside the individual's awareness. Such conflicts can be targets for successful treatment with psychodynamic therapy.

Communication-focused therapy (CFT) was developed by the author to focus on the processes which underly most forms of psychotherapy even if the particular school of psychotherapy does not focus on it. (Haverkamp, 2010, 2017b, 2017a) In this approach the patient builds awareness and insight into internal and external communication processes to find better ways to interact with himself or herself and the world. Besides raising the sense of self, efficacy and confidence, it also leads to more adaptive behaviors and interactions where own needs, values and aspirations can be more effectively pursued and fulfilled.

Evolutionary psychology

An evolutionary psychology explanation is that increased anxiety serves the purpose of increased vigilance regarding potential threats in the environment as well as increased tendency to take proactive actions regarding such possible threats. This may cause false positive reactions but an individual suffering from anxiety may also avoid real threats. This may explain why anxious people are less likely to die due to accidents.

When people are confronted with unpleasant and potentially harmful stimuli such as foul odors or tastes, PET-scans show increased blood flow in the amygdala. In these studies, the participants also reported moderate anxiety. This might indicate that anxiety is a protective mechanism designed to prevent the organism from engaging in potentially harmful behaviors.

Social

Social risk factors for anxiety include a history of trauma (e.g., physical, sexual or emotional abuse or assault), early life experiences and parenting factors (e.g., rejection, lack of warmth, high hostility, harsh discipline, high maternal negative affect, anxious childrearing, modelling of dysfunctional and drug-abusing behavior, discouragement of emotions, poor socialization, poor attachment, and child abuse and neglect), cultural factors (e.g., stoic families/cultures, persecuted minorities including the disabled), and socioeconomics (e.g., uneducated, unemployed, impoverished (although developed countries have higher rates of anxiety disorders than developing countries)).

Medication

There are basically two kinds of medication which are used to treat anxiety, the medication which is used in the short-term and is useful as standby medication to lower the anxiety about becoming anxious, but which should not be used regularly in the medium- or long-term, and the long-term medication which usually takes some time to work but which do not lead to dependence in the long-run.

A more detailed discussion can be found in the author's book *An Overview of Psychiatric Medication* (Haverkamp, 2018a).

Short-term, standby medication

Benzodiazepines

Most anxiolytics belong to the group of benzodiazepines, and although they can be very effective in reducing anxiety for up to a couple of hours, they have three main disadvantages.

The first disadvantage is that they are potentially addictive if taken regularly, the second that they do not work instantaneously and their effect only lasts for a short time, and the third that they can lead to drowsiness and a lowered reaction time, which means that a patient on this medication should not be driving a car or operating heavy machinery while taking them. If someone suffers from sudden anxiety bouts of anxiety or even panic attacks, it can be over by the time the medication starts working. However, many patients are helped quite effectively by merely having an anxiolytic in their pocket. This works because often the anxiety about feeling anxious and having all the physical symptoms associated with it is the main factor in maintaining the anxiety.

Long-term medication

In the long-term medication should be used which is not addictive and does not cause tolerance. Often it is advisable for the patient to stay on this medication for 6 months to a year, if it works, so that the brain can unlearn to be anxious, which requires neuronal as well as psychological and behavior adjustments.

Selective Serotonin Reuptake Inhibitors (SSRIs)

The long-term solution should be a combination of psychotherapy/counselling and, if indicated, an antidepressant from the group of serotonin reuptake inhibitors (SSRIs). Neurobiologically, all SSRIs can be effective in reducing anxiety and allowing even house bound patients to partake in daily life again, but a few of them are usually prescribed in practice. While they can take up to three weeks, and sometimes even more, to show their full effect, they are generally described as non-addictive and especially in the case of the newer ones, such as escitalopram, patients report few, and in many cases no side-effects. If there are mild side-effects, they often tend to go away after a couple of days. In the case of anxiety, starting with a very low dose (a quarter tablet) for two days and then increasing the dose slowly mostly eliminates subjective side-effects. In practice, if there are side effects in the beginning in the form of tension and an increase in anxiety, this often actually means that they will work. The side effects probably come from the increased serotonin levels at the synapses meeting a hypersensitivity to serotonin. A reconfiguration in the receptor density takes time, but will lead to a fading away of the symptoms and the heightened anxiety levels.

The mainstream opinion is that they can be taken over many years and are quite safe. One should pick the SSRI with the best side effect profile for the specific patients. Escitalopram, for example, is linked less with weight gain and nervousness. Sertraline can be more activating, citalopram and paroxetine more sedating. Paroxetine can be increased in dose to 60mg if OCD is also an issue. Higher doses of fluoxetine and sertraline can also be helpful if an eating disorder is a comorbid problem. However, at least in theory, in different doses all the SSRIs can have similar effects.

SSRIs can be combined with a variety of other drugs. However, they should not be combined with MAO inhibitors (antidepressants), certain neuroleptics and other medication, which can increase the serotonin level and in combination lead to the rare but potentially life-threatening serotonin syndrome. They can increase the effect of alcohol, so additional care should be taken in this regard.

Being for at least six months to a year on SSRIs often seems to have the effect, that once the medication is discontinued anxieties are less likely to return for some time. The reason does not seem to be entirely biological but also an effect of learning. As the memory of feeling anxious becomes a distant memory, one is less likely to feel anxious.

Before an SSRI is given certain conditions should be excluded in a conversation with the patient. Among them are a certain type of heart arrhythmia (abnormalities in the QT interval). If the patient is treated for a medical condition, it helps contacting the GP or specialist and asking if there are any indications the patient might suffer from a condition that may be a reason for caution.

But overall, the SSRIs, with escitalopram as a personal favorite in many uncomplicated cases, have shown to be an enormous help in treating anxiety and allowing patients to lead normal lives. In combination with psychotherapy / counselling the long-term prognosis for anxiety disorders in most cases has become very good.

Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

Venlafaxine is also licensed for the treatment of anxiety. However, since it also increases the norepinephrine levels, it could even raise anxiety levels in the beginning if the medication is started too fast. If the patient also suffers from a depression with lack of energy or pronounced concentration problems, venlafaxine may be a good choice if it otherwise fits the individual symptoms to treat both the depression and the anxiety. However, it should be started slowly from 37.5 mg, going up to 150 mg or 225 mg. Quite often there is a marked added effect between those two doses. In some cases of depression even 300 mg may be required. However, for anxiety alone lower doses can already be sufficient.

Non-benzodiazepine anxiolytics (5-HT_{1A} autoreceptor agonists)

Buspiron (Buspar®), can take weeks to unfold their anxiolytic effect and many patients do not find them as effective as the benzodiazepines. Often a better option is to start with a benzodiazepine and an SSRI and to wait until the benzodiazepine is no longer needed. For most SSRIs, this interval is in the region of two to three weeks. However, it can be much faster or in some cases even take months.

GABA analogues and other mechanisms

Pregabalin (Lyrica® and others), originally an antiepileptic, is in clinical practice often effective in the treatment of generalized anxiety disorder. It works as a GABA analogue biochemically in several ways. Increasing the dose gradually from 50 mg per day to three times 100 mg or even 150 mg per day can be very effective against anxiety in several cases. However, it is not an antidepressant and is often combined with an SSRI because many patients suffering from anxiety often also have at least a mild, possibly atypical

depression at the same time. By itself it also does not seem helpful in the treatment of the anxiety associated with obsessive-compulsive disorder (OCD).

Gabapentin also has similarities to the GABA molecule but seems to have different receptor affinities. Off-label it is also used in the treatment of generalized anxiety disorder. It may be useful in cases where pregabalin, for example, leads to increased appetite and weight gains. However, larger randomized controlled studies or meta studies on the use of gabapentin in the treatment of anxiety so far do not exist.

Conclusion

Anxiety has become highly treatable and no patient should be left to suffer from abnormal anxiety levels or panic attacks. In the majority of cases an SSRI, such as escitalopram at an upper dose, and regular psychotherapy can resolve the anxiety in several weeks to a few months. Adding a benzodiazepine for the early phase until the antidepressant works and as a stand-by medication for later phases is helpful to break the cycle of feeling anxious about becoming anxious. However, there are many other psychopharmacological options either by themselves or as add-ons to augment the anxiolytic effect of the antidepressant.



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