

## **CHAPTER 17**

### **ANXIETY TREATMENT**

#### **Introduction**

Anxiety disorders are more fully described in Chapter 19.

Here, a couple of observations are repeated - Anxiety (or its equivalents: fear, arousal, worry) is ubiquitous – it (they) have evolutionary value, alerting and motivating action (escape) in dangerous situations.

Fear is anxiety which is secondary to a stressor, such as a hungry lion – and fear usually subsides with removal of the stressor.

The anxiety disorders (also referred to as pathological anxiety) can be considered to be fear which occurs when no stressor can be identified.

For much of human history, anxiety has been (self) “treated” with alcohol and opium. These are addictive substances, and are best avoided.

The barbiturates came into clinical practice in 1903. They worked well for anxiety – however, they were highly addictive. They were also potentially fatal in overdose (because they suppressed respiration) and were discontinued as a treatment of anxiety.

#### **DSM-5**

Under the heading “Anxiety disorders” – lists 7 disorders

#### **Royal Australian and New Zealand College of Psychiatrists (2018)**

Published treatment guidelines for

1. Social anxiety disorder (SAD)
2. Panic disorder, and
3. Generalized anxiety disorder (GAD)

#### **Common treatment components**

Across all psychiatric disorders, two treatment components are applied. In the first instance assistance is verbal – including information/education and psychotherapy.

When verbal assistance does not provide sufficient improvement, physical treatments are added – such as medication are added.

A general mention will be made of verbal treatment and medicines – followed by specific information regarding these 3 disorders mentioned above.

## VERBAL TREATMENT

### Psychoeducation

Providing the patient with information about their disorder is part of the management of most disorders. When patients learn about the anxiety disorder they are suffering they feel less isolated and demoralized and more positive. Even basic information may strengthen the patient and render the symptoms less apparent and painful.

RANZCP (2018) also recommends patients improve their general health – reducing caffeine and alcohol, taking a healthy diet and regular exercise and regular sleeping habits.

Basic information on relaxation and slowing the breathing rate at the first sign of increased arousal provide mechanisms for treating/managing symptoms.

The patient should be informed and involved in treatment decisions – this improves the sense of ownership and potency, increasing the chances of success.

### Psychotherapy

Psychotherapy has taken many forms over the last century.

**Psychoanalysis** founded by Sigmund Freud (1856-1939) was the earliest – the aim was to release repressed emotions and experiences. It is time consuming and not much practiced at the present time. **Psychodynamic psychotherapy** is still practiced and has roots in psychoanalysis.

Other forms have come and largely disappeared, including, **Client-Centered Therapy**.

**Relaxation** and **mindfulness** psychotherapy are currently practiced. **Acceptance and Commitment Therapy (ACT)** has recently emerged and may have an important contribution over time.

**Cognitive behaviour therapy (CBT)** is a current leading example, is effective in the treatment of anxiety. Different authors may include different components under this heading – some include relaxation and education.

The unique component of CBT is the understanding that our thinking (what we are telling ourselves) greatly influences how we feel. The treatment is helping the patient recognize and correct illogical thinking habits – “If this person isn’t attracted to me, I must be ugly and should kill myself”. CBT has its roots in Greek Stoic Philosophy – which makes arguments such as – “Don’t feel bad about things you can’t change” and “desiring/wanting physical things leads to unhappiness”. CBT is a skilled practice and therapists require supervised training.

In addition to face-to-face CBT useful self-help books teach the CBT principles. Also, digital (d)CBT via various devices provides structured instruction.

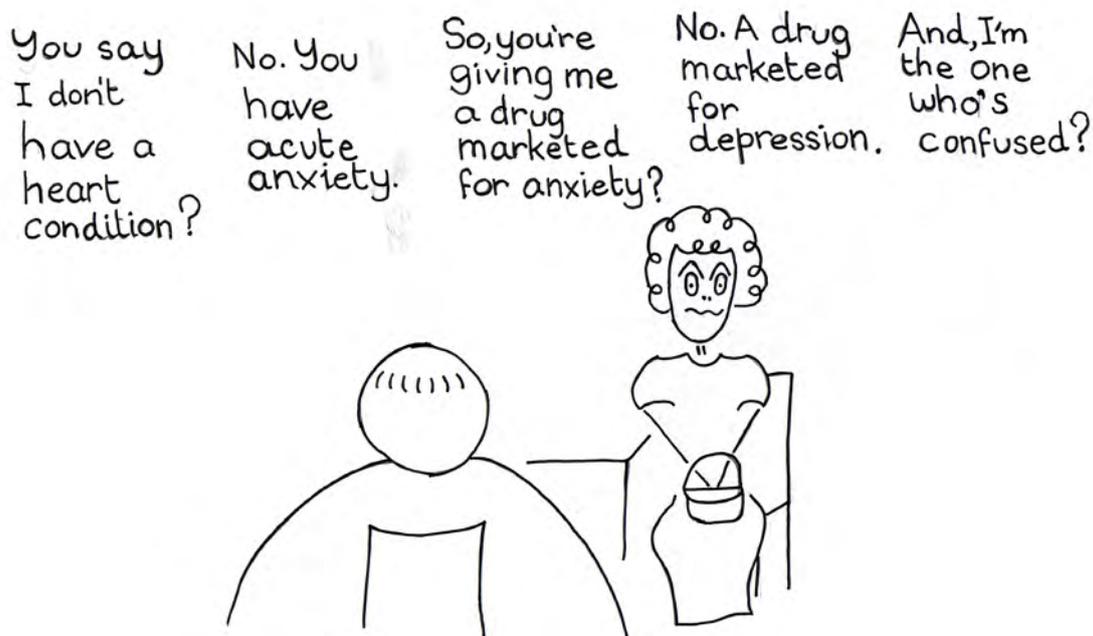
There is no evidence to support the claims that CBT is superior to pharmacotherapy in the treatment of anxiety disorders, that CBT combined with pharmacotherapy provides double the therapeutic effect, or that CBT has a long lasting effect, persisting well beyond the treatment period.

However, CBT has been studied more than any other psychotherapy and efficacy has been demonstrated by numerous meta-analyses (Craske and Stein, 2016).

## PSYCHOPHARMACOLOGY

### SEROTONIN REUPTAKE INHIBITION (SSRIs & SNRIs)

These drugs have been described in Chapter 16: Antidepressant drugs.



This joke is funny to old doctors who remember when the benzodiazepines were universally marketed as THE anxiolytic drugs. Eventually they were replaced by the SSRIs which had been universally marketed as THE antidepressant drugs. This patient presented to the doctor with a rapid heart rate – she thought she had heart disease - the doctor explained that she had an anxiety disorder - and that he would treat it with an antidepressant.

The selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenalin reuptake inhibitors (SNRIs) are described in detail in the Chapter 16: Antidepressant drugs.

These medications are the first-line therapies for anxiety disorders (Bandelow, 2014; Craske & Stein, 2016). Their effect is independent of the presence of depression. The effective dose in anxiety treatment is frequently higher than used in the treatment of depression.

The antidepressants have the advantage of not being of being non-addictive, and of no interest to drug traffickers.

A meta-analysis of generalized anxiety treatments (Baldwin et al, 2011) found **fluoxetine** (SSRI) was superior to various other drugs (including a benzodiazepine) in achieving response and remission; and that **sertraline** (SSRI) was the best tolerated. **Escitalopram** (SSRI) is effective and well tolerated according to another meta-analysis (Slee et al, 2019) – but, this is not the clinical experience of the current author.

**Paroxetine** has anxiolytic properties, but is not well tolerated (Slee et al, 2019).

The disadvantage of the SSRIs (relative to the benzodiazepines) is that the onset of beneficial effect may take some weeks. In addition, there may be an initial, temporary worsening of anxiety. It has been stated that the SSRIs are associated with increased suicidality (Hjelmeland et al, 2018) – more work is needed on this point.

**Venlafaxine** and **Duloxetine** (SNRIs) are effective in the treatment of anxiety (Slee et al, 2019). They are not without side-effects and withdrawal symptoms, but like the SSRIs, they are of no interest to drug traffickers.

## **BENZODIAZEPINES**

The first of the benzodiazepine family medications (antianxiety and hypnotic agents) became available in 1960 - many others followed – small amounts continue to be used.

The benzodiazepines have a rapid onset and are highly effective. However, they can be abused in which case, addiction can occur. There are also claims they are associated with cognitive impairment and falls (limited to the elderly), dizziness and ataxia have been mentioned – thus, use is discouraged (RANZCP, 2018).

The benzodiazepines potentiate the actions of the widespread inhibitory neurotransmitter, gamma-aminobutyric acid (GABA).

The GABA A receptor is the gate keeper of a chloride channel. The benzodiazepine receptor is on the same protein molecule as the GABA A receptor. When a benzodiazepine occupies a benzodiazepine receptor, there is allosteric modulation of the GABA A receptor, such that the arrival of a molecule of GABA triggers the passage of a greatly increased quantity of chloride through the channel. Thus, the benzodiazepines are effective inhibitors because they make the endogenous inhibitor (GABA) more effective.

The benzodiazepines are safe in overdose - superior to their predecessors in this regard.

### The great benzodiazepine debate

As mentioned, the benzodiazepines were introduced in the 1960s and were the drug of first choice in the treatment of anxiety disorders for forty years. Then various problems are reported including falls among the elderly and motor vehicle accidents (Bolton et al, 2008). The potential for abuse and addiction had been known.

Authoritative reviews/guidelines focused on these public health issues and recommend against benzodiazepines use (Bandelow et al, 2014).

There was a strong reaction and support expressed for the benzodiazepines. Rickels (2013) - 'There is no evidence of superiority of newer antidepressants over the benzodiazepines in either long or short term treatment of anxiety. Benzodiazepine toxicity, adverse events and withdrawal symptoms, not better efficacy are cited in support of antidepressants over benzodiazepines; but the antidepressants are no better tolerated and also produce withdrawal symptoms.'

Recent work suggests concerns of misuse are overrated. Blanco et al (2018) report that in the USA, while 12.5% of the population use benzodiazepines only 1.5% of this group misused their medication. (Of the total population, 0.2% misused benzodiazepines.)

It is difficult to understand how this disagreement in the place of the benzodiazepines emerged. However, as guidelines continue to be released recommending in favour of the antidepressants and against the benzodiazepines (RANZCP, 2018) and so, we must lean in that direction.

As an aside – some decades ago, a common criticism of doctors was that they did not listen to their patients, especially their female patients - and instead, prescribed them “Valium” as a disrespectful, easy solution.



Illustration. Valium Spray, for general household uses: fighting, baby sitting, quietness, peace. This drawing was given to the author as a gift by a young female patient in 1998. The author believes the patient's conscious motives were positive. The reader may speculate about her unconscious motives.

### Example drugs

There is a large range of benzodiazepines, with different potencies and half-lives.

The advantages of the long-acting drugs include less frequent dosing, less variation in plasma concentration, and less severe withdrawal. The disadvantages of the long-acting drugs include drug accumulation, and increased risk of daytime psychomotor impairment and drowsiness.

The advantages of the short-acting drugs include no drug accumulation and less daytime sedation. The disadvantages of the short-acting drugs include more frequent dosing and earlier and more severe withdrawal syndromes. Rebound insomnia and anterograde amnesia are thought to be a greater problem with the short-acting drugs.

**Diazepam** is a long acting drug; usual daily dose 5-40 mg. Can be given once daily, but is given in divided doses when using large doses.

**Clonazepam** is a long acting drug; usual daily dose 1.5-10 mg. Can be given once daily, or in divided doses.

**Oxazepam** is an intermediate acting drug; usual daily dose 30-60 mg. Usually given in divided doses, three times daily.

**Temazepam** is an intermediate acting drug which is exclusively marketed as an hypnotic. The usual nocte dose is 10 mg, but 20 mg is also used.

**Alprazolam**, which is structurally distinct from all other benzodiazepines, is given a separate paragraph because it has a relatively high potential for abuse. In many jurisdictions it is listed along with the highly restricted drugs (narcotics).

### BUSPIRONE

Buspirone was hailed some decades ago as the new non-benzodiazepine treatment of anxiety. While Slee et al (2019) found buspirone to be efficacious and well tolerated – the RANZCP (2018) states that for SAD, “buspirone...should not be used” (page 1139). When ‘expert’ opinions clash – ask the advice of experienced local clinicians.

Buspirone is a 5HT-1A partial agonist. It suppresses activity in presynaptic serotonergic neurons, leading to diminished serotonin activity and down-regulation of some serotonin receptors. It has no muscle relaxant properties, no psychomotor or cognitive impairment, and is less sedating than the benzodiazepines. It does not potentiate the effects of alcohol (as can the benzodiazepines) and there is no withdrawal. The side-effects include headache, dizziness and nausea.

In formal clinical trials, buspirone was as effective as diazepam (Fulton & Brogden, 1997) – this has not been replicated and is almost certainly wrong. The main clinical disadvantage is that the anxiolytic effect does not appear immediately, and may be delayed for at least 2 weeks – while the benzodiazepines have an immediate effect. A second disadvantage is that buspirone is much less effective when the patient has had prior exposure to a benzodiazepine. In clinical practice, and certainly when a rapid response is required, buspirone is rarely used in the treatment of anxiety (Hodge et al, 2012).

## **BETA-ADRENERGIC ANTAGONISTS**

The use of beta-blockers in the management of anxiety disorders has not been examined in meta-analyses. These drugs have not been addressed in guidelines for the treatment of anxiety. These facts are surprising given that beta-blockers are commonly prescribed (albeit to augment the effects of other medications) in clinical practice to reduce anxiety related palpitations.

The first systematic review and meta-analysis of propranolol in anxiety disorders (Steenen et al, 2016) found the effects of propranolol to be similar to the benzodiazepines.

The beta-blockers are widely used in the management of “normal anxiety” – when there is arousal which may interfere with performance. Orchestral performers, such as violinists troubled with trembling fingers frequently benefit from beta-blocker use.

In a related manner, beta-blockers are widely used by students taking high school exams. From Denmark, Butt et al (2016) characterized >12 000 students who so used beta-blockers.

Where the symptoms are predominantly somatic and mediated by the sympathetic nervous system (palpitations, tremor and gastrointestinal overactivity), beta-blockade has been suggested.

Most authorities no longer recommend the use of beta-blockers in the treatment of anxiety – but, it does occur in clinical practice.

## **PREGABALIN**

**Pregabalin** is an anticonvulsant which is used in the treatment of pain disorder. It is structurally related to GABA. It is believed to inhibit calcium channel activity, leading to reduced neurotransmitter release, which in turn leads to reduced postsynaptic neuron excitability.

Early studies suggested anxiolytic effects comparable to the benzodiazepines. There was great excitement because the abuse potential appeared to be small. Recent Australian work (Crossin et al, 2019) indicate a marked euphoric effect, and high potential for abuse and black-market value. It is unlikely to be marketed as an anxiolytic

RANZCP (2018) places gabapentin (related) among medications which may be tried when the patient has failed to respond to standard treatments – with the caveat – “There is limited evidence supporting the use of these medications either as monotherapies or adjunctive therapies” (page 1133). But, also provides some support (pages 1147 & 1150).

## ANTIPSYCHOTICS

Antipsychotic medications (quetiapine etc) have been used in the treatment of anxiety disorders (Hershenberg et al, 2014). However, due to potential serious side effects, including weight gain, metabolic syndrome and prolonged QTc syndrome, use is not recommended (RANZCP, 2018, page 1139, 1148 & 1153).

However, some support can be found for the use of antipsychotic drugs across the anxiety spectrum (Albert et al, 2016).

## CANNABIS

Cannabis provides euphoric and relaxing effects. It is probable that some cannabis use is a form of self-medication for the treatment of pathological anxiety. However, people with anxiety disorders generally advised to avoid cannabis.

Interestingly, in Canada 'cannabis for medicinal purposes' (CMP) is provided to people with anxiety disorders and they report satisfaction (Turna et al, 2019).

## HYPNOTICS

### Benzodiazepines

**Temazepam** and **nitrazepam** continue to be marketed as hypnotics

### Benzodiazepine-like hypnotic

**Zolpidem** is a non-benzodiazepine hypnotic which potentiates GABA by binding to the benzodiazepine receptor. Most frequently used hypnotic in the USA. It is effective in sleep initiation, but less effective in sleep maintenance.

Dependence is known. Transient memory problems and, in depressed individuals, worsening of suicidal thinking, have been reported.

A study at the Mayo Clinic showed zolpidem significantly increases the risk of falls, and it is being discontinued at that hospital (Voelker, 2012). MacFarlane et al (2014) found that 'zolpidem is associated with rebound insomnia, complex sleep-related behaviours, and next-day residual effects (after middle-of-night dosing) on driving ability, memory and psychomotor performance'.

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