



Prescribing where there is a comorbid presentation of anxiety and depression: a case study

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ABSTRACT:

Everyone experiences symptoms of anxiety during their lifetime. It is a normal physical or psychological response to stress, mediated through adrenaline (epinephrine) and noradrenaline (norepinephrine). Anxiety disorders are extreme or pervasive versions of this response, and include a spectrum of different conditions (NICE, 2019).

In the UK, approximately 15-20% of the population experience an anxiety disorder at some stage in their life, and there is evidence that women are more prone to anxiety disorders than men (Bentall, 2016). However, despite their prevalence anxiety disorders can be difficult to diagnose accurately as they are often co-morbid with each other, or with other mental illnesses. They also frequently, present as physical illnesses. They also frequently present as physical illnesses such as heart, or gastrointestinal conditions.

Co-morbidity is often a feature of complex mental health presentations, and the author uses a case study to show how non-medical prescribing formulations, and basic pharmacology, relate to clinical practice.

The case study considers a complex presentation of anxiety, with associated depression and describes the stepped care approach to care and treatment advocated by the National Institute for Health and Clinical Excellence.

Accurate medical/clinical diagnosis of a person's specific anxiety disorder can help them understand their condition and ensure that they are offered the most appropriate treatment at the earliest opportunity. The Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) is the most widely accepted framework and nomenclature used by clinicians and researchers for the classification of mental disorders and is referred to in the case study.

Mixed anxiety and depression is a common presentation in primary care characterised by a mix of anxiety and depressive symptoms without clear prominence of any one type and the presence of one or more physical symptoms, such as tremor, palpitations, lethargy etc, that are present for more than six months (Gask et al, 2018).

Anxiolytic medication is often used as a first aid measure in anxiety and is very useful and appropriate for this. It is, however, quite difficult to assess the longer-term effectiveness of these drugs as anxiety tends to vary for reasons other than drug treatment such as external pressures. Long-term use of benzodiazepine drugs is generally not advised, for addiction/dependence reasons, and some people do get some withdrawal effects if they stop benzodiazepines suddenly, so when the time comes to stop, it is best to reduce the dose slowly.

There is good evidence (Hofmann, 2018 and NICE, 2019) to support the efficacy of psychological interventions in anxiety spectrum disorders.

Consequently, self-help and CBT may be the first line of treatment for less severe cases and can be used in conjunction with medication. General support and information about the condition, with an empathic understanding of the life circumstances that may be contributing to the anxiety can be helpful.

INTRODUCTION

People with anxiety can have a variety of symptoms (NICE, 2011). These can be divided into two main groups, psychological and physical. Psychological symptoms: include fear, irritability, poor concentration, restlessness, sensitivity to noise, disturbed sleep, such as waking during the night, unpleasant dreams etc and poor memory usually due to poor communication. Physical symptoms: are mainly due to increased muscle tension e.g. problems with passing wind, loose motions, blurred vision, dizziness, loss of libido, breathing problems such as tight chest, difficulty breathing, heart changes, such as palpitations, heart pain or missed beats, tension resulting in headache or tremor and panic attacks leading to sudden episodes of extreme anxiety or apprehension. This is due to overactivity of many parts of the brain, usually caused by some external pressure or reason. The symptoms may be caused by this overactivity. The result is that many systems in the body become overactive e.g. muscle control, thinking, worrying etc (Tovote et al, 2015).

The action of anxiolytic medications

Although there are over 80 known different transmitters in the brain, each nerve ending only has one type. These neurotransmitters tend to be grouped together and each seems to have specific roles. In many mental health problems, it is known that some of these transmitters get out of balance e.g. if someone has an insufficient amount of a particular transmitter. This can then cause symptoms. (Tovote et al, 2015 and Blows, 2016).

Epinephrine (E) and norepinephrine (NE) are very similar neurotransmitters and hormones, and both play a role in the body's natural fight-or-flight response to stress. Norepinephrine (NE), previously called noradrenaline (NA), in the body controls the heart and blood pressure. In the brain it controls sleep, wakefulness, arousal, mood, emotion and drive (wakefulness/sleep wake behaviour). Too much norepinephrine and someone may feel anxious and jittery etc. Too little and they may feel depressed, sedated, dizzy, or have low blood pressure. However, GABA is the key transmitter, in relation to anxiety as it is the brain's natural calming agent. It acts as a brake in the brain and keeps its activity in check. When someone is overanxious, it may be that not enough GABA is being released in the brain to help calm it down. Drugs such as the benzodiazepines, zopiclone and zolpidem increase the length of the action of the GABA. This helps calm down the brain and reduces the number of worrying messages being passed.

A benzodiazepine drug binds to the GABA and acts as an agonist for the inhibitory neurotransmitter to GABA. In that sense it mitigates against the

sudden reduction in available GABA, which can trigger panic, restlessness, insomnia, and potentially convulsions or seizures.

Benzodiazepines block GABA in its receptors, so the receptors are activated for longer, and so the brains natural calming messages are passed stronger (LeDoux, 2000 and 2015, and Blows, 2016).

The important thing to remember is that anxiolytic medication mainly works by strengthening the brains natural calming agents, but they should not be considered just as tranquillisers although they may help someone to feel calmer, as they have a much more specific way of working, than simple sedation (LeDoux, 2015, and Blows, 2016).

Why do people get side-effects?

These drugs block GABA into its receptors, so the receptors are activated for longer, and so the brains natural calming messages are passed with more strength. GABA is widespread throughout the brain, and so a few adverse side effects are due to this more generalised sedation, e.g. confusion etc.

These should be able to be minimised by adjusting the dose. Some benzodiazepines are also used for helping treat epilepsy, as calming drugs before operations, and as muscle relaxants (LeDoux, 2015, and Blows, 2016).

CASE STUDY

Sonia, a 37-year-old mortgage-broker, has an appointment at her local GP surgery, to see Derek (Advanced Nurse Practitioner) and arrives with Nathan her 7-year-old son who has been diagnosed with type 1 diabetes. Sonia lives with her husband in her own 3-bedroom house. The woman appears tremulous and becomes tearful while talking about her son's condition. She

says that she has been very worried about her son and has not been sleeping very well for the past 5-6 months, though she has been eating reasonably well, although she admits that she has felt more tired and demotivated than usual.

Sonia is still going to work but has found it hard to concentrate on her duties as well as before. Because of this she constantly worries that she might make a serious mistake at work. She says that she has managed to cope with the support of her husband. However, he also works full-time and there have been days when she has found it difficult to get out of bed. Currently Sonia feels that she is going through a bad patch and is hopeful that things will get better soon. She does not see a problem with her self-esteem and finds her work enjoyable but exhausting.

When asked, Sonia completely dismisses any idea of self-harm or suicide and says she would never even think about it. She apologizes profusely to Derek for becoming emotional and asserts that she is normally very calm and composed but has become overwhelmed by the stress of her son's illness.

In relation to herself, she denies history of any mood episodes, either depression, or hypomania. She drinks alcohol socially, never exceeding 8 units per week. She does not smoke or use any illicit drugs. She describes herself as 'driven' and 'ambitious'. She is a keen runner and runs 14-18 miles a week.

She agrees to a brief physical examination. She has tachycardia of 108/min, her pulse is regular, and her blood pressure is 138/88 mmHg. Her palms appear cold and sweaty but there is no other significant physical finding.

Sonia is pleasant, co-operative and Derek is able to quickly establish a good rapport with her. She is clutching her son protectively but maintains good eye-to-eye contact throughout the interview. Her speech is at a normal rate and volume. Her mood is anxious and low. She does not have any psychotic symptoms. Sonia has a good insight into her symptoms.

She does not have any ideas of self-harm, but Sonia reveals that two years ago, she 'borrowed' some anxiety and sleeping pills from her mother who kept a stock-pile of drugs for emergencies. Sonia remembers the names Ativan and Zolpidem, from the drug boxes, but cannot recall the doses, and how regularly she took the pills.

Sonia asks if she can be prescribed a benzodiazepine drug, and some sleeping tablets. She says her husband thinks this would be a good idea.

DISCUSSION

There are many possible explanations as to why women such as Sonia develop anxiety disorders more frequently than men (Carver & Connor-Smith, 2010). Women are more likely to communicate their feelings and it is culturally more acceptable for women to feel anxiety. This makes it easier for them to seek help, for the symptoms they might be experiencing. It could also be due to men being more likely to self-medicate with substances such as alcohol in an effort to mask anxiety symptoms (Freeman and Freeman, 2013).

Applying the Global Mental Health Assessment Tool (Sharma, 2004) Sonia is presenting with a mixture of anxiety and depression and depressive symptoms occurring in the context of her son's illness. She is feeling very stressed and increasingly reliant on her husband for support.

Medical/clinical diagnostic possibilities include:

Mixed anxiety and depression: This is a common presentation in primary care characterized by a mix of anxiety and depression symptoms without clear prominence of any one type and the presence of one or more physical symptoms typically tremor, palpitations, and lethargy present for more than 6 months (NICE, 2009 and 2019).

Depression: Sonia does have the core symptoms, namely low/anxious mood, reduced energy and some other symptoms such as reduced concentration and poor sleep lasting more than two weeks suggesting a mild depressive episode.

Bipolar disorder: needs to be excluded by asking about hypomanic/manic episodes (Paris, 2012). Detailed history and mental state examination will be needed to establish the diagnosis and appropriate investigations to rule out any medical disorders will also be required.

NICE guidelines (2009) suggest that when depressive and anxious symptoms coexist, the first priority should usually be to treat the depression.

Psychological treatment for depression often reduces anxiety, and many antidepressants also have sedative/anxiolytic effects. The guidelines advocate a stepped care approach, which is a system of delivering and monitoring treatments so that the most effective, but least resource-intensive treatment is delivered first. NICE support the use of Cognitive Behaviour Therapy (CBT), but not other psychodynamic psychotherapies (NICE, 2009).

The advice for mild depression does not help in uncertain decisions when a particular case may or may not benefit from medication, but this reflects the evidence available (Beck, 2009). These milder presentations may be subthreshold disorders where health professionals allow the “*medicalisation of unhappiness*” (Burns, 2013). In order to legitimise the engagement, when all that people may really need in these times of growing social isolation is some or more support (Carver & Connor-Smith, 2010).

Sonia is ambitious, energetic, and committed to supporting her family, and succeeding in her career, but, in the short-term at least, she might benefit from some self-compassion. Kindness and concern for self is recognised element of healing and mental health recovery (Lazarus, 2006). Therefore, Sonia might be encouraged to attend a local peer-support group, and/or relaxation classes. Social interventions like this should be viewed as ‘protective’ factors that potentially might be helpful in mitigating risk and relieving some of the fear, distress and inertia associated with many presentations of anxiety and depression (Aspinwall & Taylor, 1997). Also, it is possible that Sonia’s symptoms might dissipate, once she is assured that her son’s condition is manageable. This might require some education about Type 1 diabetes, but potentially, it might benefit both Sonia and her child.

A stepped care model approach (NICE, 2019) would be well suited to Sonia’s situation, as she has mild mood symptoms and as per the stepped care model, these are best treated initially, in a primary care setting (Tolin et al 2011).

Watchful waiting, i.e. a follow-up appointment within two weeks with reassurance is sensible as symptoms may resolve spontaneously but if Sonia’s symptoms persist on subsequent visits, brief psychological

interventions may be provided by either a primary care mental health

**A stepped care model adapted from the National Institute for Health and
Care Excellence guidelines for the management of depression**

practitioner or a practice counsellor.

<p>Step 1</p> <p>Mild or suspected depression</p>
<p>Assess, support, provide psycho-education, monitor and refer onwards as appropriate</p>
<p>Step 2</p> <p>Mild to moderate depression</p>
<p>Consider interventions to address psychosocial problems</p> <p>Psychological interventions (e.g. Cognitive behaviour therapy, self-help resources)</p> <p>Antidepressant according to the patient's wishes and preferences</p>
<p>Step 3</p> <p>No response or moderate to severe depression</p>
<p>Medication</p> <p>High intensity psychological interventions</p> <p>Combined treatments and referral for specialist input as appropriate</p>
<p>Step 4</p> <p>Severe and complex depression</p> <p>Risk to life</p> <p>Severe self-neglect</p>

Medication and/or electroconvulsive therapy

High-intensity psychological interventions

Crisis service, combined treatments, multi-professional and inpatient care

Motivational interviewing might also help Sonia change her behaviour (Miller & Rollnick, 2013). Computerized cognitive behaviour therapy can also be helpful (Arnberg et al, 2014) and also healthy lifestyle advice about exercise and sleep hygiene. Guided self-help using manuals or self-help books are other options available in primary care (Davidson et al, 2016).

If Sonia's symptoms worsen, treatment can be commenced taking into account her preferences. Psychological treatments such as Cognitive Behaviour Therapy (CBT) or antidepressant/anxiolytic medication such as Selective Serotonin Reuptake Inhibitors (SSRIs) can be effectively administered in primary care (Hofmann & Smits, 2008 and Hofmann, 2018).

Treatment-resistant cases, psychotic symptoms, atypical symptoms or recurrent episodes should trigger a referral to specialist services. At any stage, if risk profiles change rapidly and risk assessment indicates a risk to self, others or self-neglect a referral can be made to the crisis team for consideration of inpatient treatment (NICE, 2019).

Given Sonia's revelation about the lorazepam, it is necessary to gently remind her of the importance of only taking medication, that has been prescribed, and particularly the risks associated with long-term, unsupervised use of

benzodiazepines, such as psychological addiction, dependence and withdrawal (Taylor et al, 2018).

Her self-medication, with unprescribed drugs, could be interpreted as a form of safety behaviour. In the context of clinical anxiety, safety behaviors are actions performed to prevent, escape, or minimize feared catastrophes and/or associated distress (Rachman et al, 2008). Developing some “positive” safety behaviours, is something that needs to be discussed with Sonia, as part of her treatment/care plan, as these can reduce risks of relapse (Goetz, 2016), which for Sonia might be the temptation of taking unprescribed medication at some point in the future.

Cases such as this one, where there is comorbidity, are associated with worse health outcomes (Miller et al, 2011), therefore, Derek, the Advanced Nurse Practitioner should speak to a GP urgently, to discuss an appropriate treatment plan for Sonia, and to confirm the diagnosis. Effective inter-disciplinary team working, is necessary to manage complex cases safely, and maximise wellbeing for service users and their families (Bailey, 2012). In the circumstances, Derek is right to be cautious about prescribing a benzodiazepine drug.

How should benzodiazepines be used?

Benzodiazepines are used in the treatment and management of pathological and chronic anxiety, agitation and tension (NICE, 2019). They act rapidly and are very useful first aid measures. However, they will only form a small part of overall management, of such conditions and may help the person until other

anxiety management techniques, e.g. psychotherapy etc. can be carried out. NICE recommends (cited by Taylor et al, 2018) that “*benzodiazepines should not be used to treat panic disorders*” and “*should only be used ‘with care’ in post-traumatic stress disorder*”.

Acute anxiety should not be assumed to be present for more than a month and benzodiazepines should not be lightly prescribed for longer than this, as benzodiazepines are known to enhance GABA transmission and also inhibit microsomal enzymes (Barlow, 2002 and Blows 2016).

Some patients, especially those with chronic anxiety, have a tendency to self-treat/medicate and benzodiazepines should be avoided in patients with a history of drug or alcohol abuse. When benzodiazepines are used, those with a slower onset of action, such as GABA partial-agonist Clonazepam, may cause less dependence than Diazepam or Lorazepam (Taylor et al, 2018). Concern has been expressed that some anxiety drugs, such as Alprazolam (Xanax) and Diazepam (Valium) have been used in many fatal/non-fatal drug overdoses (Cutcliffe & Santos 2012).

Side-effects of benzodiazepines

Headaches, confusion, ataxia, dysarthria, blurred vision, gastrointestinal disturbances, jaundice, amnesia and paradoxical excitement are all possible adverse side effects of benzodiazepines, although drowsiness is the only

common side effect (Taylor et al, 2018). Respiratory depression is rare with normal dose oral therapy but may be an added complication with sleep apnoea. It must be looked out for when the IV route is used, especially with midazolam. The IV injection can be painful and lead to thrombophlebitis due to the low water solubility of benzodiazepines (Taylor et al, 2018). Diazepam is available in an emulsion form (Diazemuls) to overcome this problem. Benzodiazepines are poorly absorbed from the IM route and the rectal route (e.g. with diazepam rectal tubules) is an appropriate alternative (BNF, 2020).

Comparative doses

The dose(s) of each drug below is approximately equivalent to others. Inter-patient variability, different half-lives (a particular problem with the benzodiazepines) make exact calculations difficult.

Table 1: Benzodiazepines/comparative doses (after BNF, 2020)

Diazepam	5mg
Chlordiazepoxide	15mg (10-15)
Clobazam	10mg
Flunitrazepam	0.5mg
Flurazepam	7.5mg – 15mg
Loprazolam	0.5mg – 1mg
Lorazepam	0.5mg
Lormetazepam	0.5-1mg

Oxazepam	15mg (15-40)
Nitrazepam	5mg (5-20)
Temazepam	10mg

Benzodiazepine dependence

Dependence is characterised by a strong need to continue taking a drug, a tendency to increase the dose, a psychological dependence on the effects of the drug and a characteristic abstinence syndrome. All of these have been reported to occur with the benzodiazepines (Bandelow et al, 2015). It has been pointed out that withdrawal symptoms are, in the milder states, very similar to acute and chronic anxiety and may be in fact a reappearance of the original symptom.

Table 2: Dependency/symptoms of withdrawal (after Taylor, et al 2018)

Primary

<i>Psychological</i>	Tension, restlessness, agitation, panic attacks
<i>Physical</i>	Dry mouth, tremor, sweating, sleep disturbance, lethargy, headache, nausea
<i>Mental</i>	Impaired memory and concentration
Secondary	
<i>Moderate</i>	<p>Perceptual changes (hyper-sensitivity to light/sound)</p> <p>Dysphoria, flu like symptoms, anorexia, sore eyes.</p> <p>Depersonalisation, depression, abnormal sensations of movement.</p>
<i>Severe</i>	Convulsion, psychoses, (e.g. visual hallucinations, delusions)

Box 1: Risk factors for poor withdrawal (after Taylor, et al 2018)

- Previous severe withdrawal (including a history of seizures) or post-withdrawal reaction
- Lack of adequate social support
- Elderly or infirm
- History of inappropriate use of alcohol or other drugs of dependence
- Concomitant severe medical biological or psychiatric illness (including personality problems)

Management of benzodiazepine withdrawal

Controlled withdrawal may take a long time with only small reductions in dosage every seven days or so being tolerated. All symptoms tend to be worse with the shorter-acting or high potency drugs (particularly lorazepam) (Taylor, 2018).

It is usual to transfer a patient onto a longer-acting drug e.g. Diazepam, and reduce the dose of that drug at a rate the patient finds acceptable (NICE, 2019).

Many people find difficulty in completing these withdrawal programmes and long term support is essential. The withdrawal syndrome has been reported to last for up to a year or longer (Rogers et al, 2007).

Hypnotic drugs for sleep problems

Such drugs may be useful in the short-term, but it is quite difficult to assess the longer-term effectiveness of these drugs as sleep tends to vary for reasons other than drug treatment e.g. external pressures etc (Klink, 1992).

If it is decided that someone requires a hypnotic drug for a long time, rather than just when they need it, this should be discussed, by the clinical team (NICE, 2004). Crucially, some people do get some withdrawal effects if they stop hypnotics suddenly e.g. rebound insomnia (Taylor et al, 2018). When the time comes to stop, it is best to reduce the dose slowly.

Other anxiolytic medication

Buspirone is licensed for the short-term treatment of anxiety. It does not act on benzodiazepine receptors but is thought to act at specific serotonin (5-HT) receptors (Taylor, 2018). Response to treatment is slow, taking 4-6 weeks to reach maximum effect making it unsuitable for as required PRN use.

However, the dependence and abuse liability of buspirone is low. Beta-blockers (e.g. propranolol) do not affect psychological symptoms, such as worry, tension and fear, but they can reduce the physical symptoms of anxiety such as heart palpitations and hand tremor (BNF, 2020). Pregabalin is an anti-convulsant used for the treatment of certain types of epilepsy. It is also licensed for the treatment of generalised anxiety disorder. (BNF, 2020).

CONCLUSION

We all experience symptoms of anxiety during our lifetime, and it is a “normal” physical and psychological response to stress, mediated through adrenaline (epinephrine), noradrenalin (norepinephrine), and GABA (LeDoux, 2001 and

2015). As we have seen, anxiolytic medication blocks GABA into its receptors. GABA is widespread throughout the brain, and so a few side-effects are due to this more generalised sedation, especially with a hangover effect the next morning possible with some drugs e.g. nitrazepam.

Anxiety disorders are extreme or pervasive versions of this response and include a spectrum of different conditions. In the UK, approximately 15-20% of the population experience an anxiety disorder at some stage of their life (Bentall, 2016). These can, however, be difficult to diagnose and treat accurately as they are often co-morbid with each other or with other mental illnesses. They also frequently present as physical illnesses, such as heart or gastrointestinal conditions (Barlow, 2002).

Key opportunities for Integrated Care Systems and mental health have been identified as: preventing ill health, linking physical and mental health and improving mental health services (Centre for Mental Health, 2020). Without changes to prescribing practice, it is difficult to see how these ambitions, can be met. This in term requires effective multi-disciplinary and interprofessional working, and person centred care.

Prescribing medication for anxiety is fraught with difficulty and prescribers should endeavour to keep an open-mind, in relation to useful alternatives or adjuncts to drug therapy (Barker, 2011). It is vital to fully explore the various treatment options, listening to the patient/client, acknowledging their preferences, and responding sensitively to any concerns they might have about drug side-effects (Moscarello & Hartley, 2017). When it comes to medicating anxiety, one size does not fit all.

Key Points (Box 2)

- The symptoms of anxiety can be reduced by increasing the strength of the brains natural calming messages.
- Anxiolytic medication helps by increasing the strength of the brains natural calming messages.
- They are not 'just tranquilisers' although they may help someone feel calmer.
- They do not directly alter personality.
- Anxiolytics are not necessarily addictive, but it is best to stop them slowly if taken for more than about a month.
- They do 'not' appear to lose their anxiolytic effect if someone stops taking them.

CPD reflective questions (Box 3)

- What risks are associated with long-term use of benzodiazepine drugs?
- Reflect on the NICE, stepped-care model for mental health. How might you utilise the framework, to inform your own prescribing practice?
- Consider alternatives to drug therapy in relation to anxiety. What are their strengths and limitations?

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