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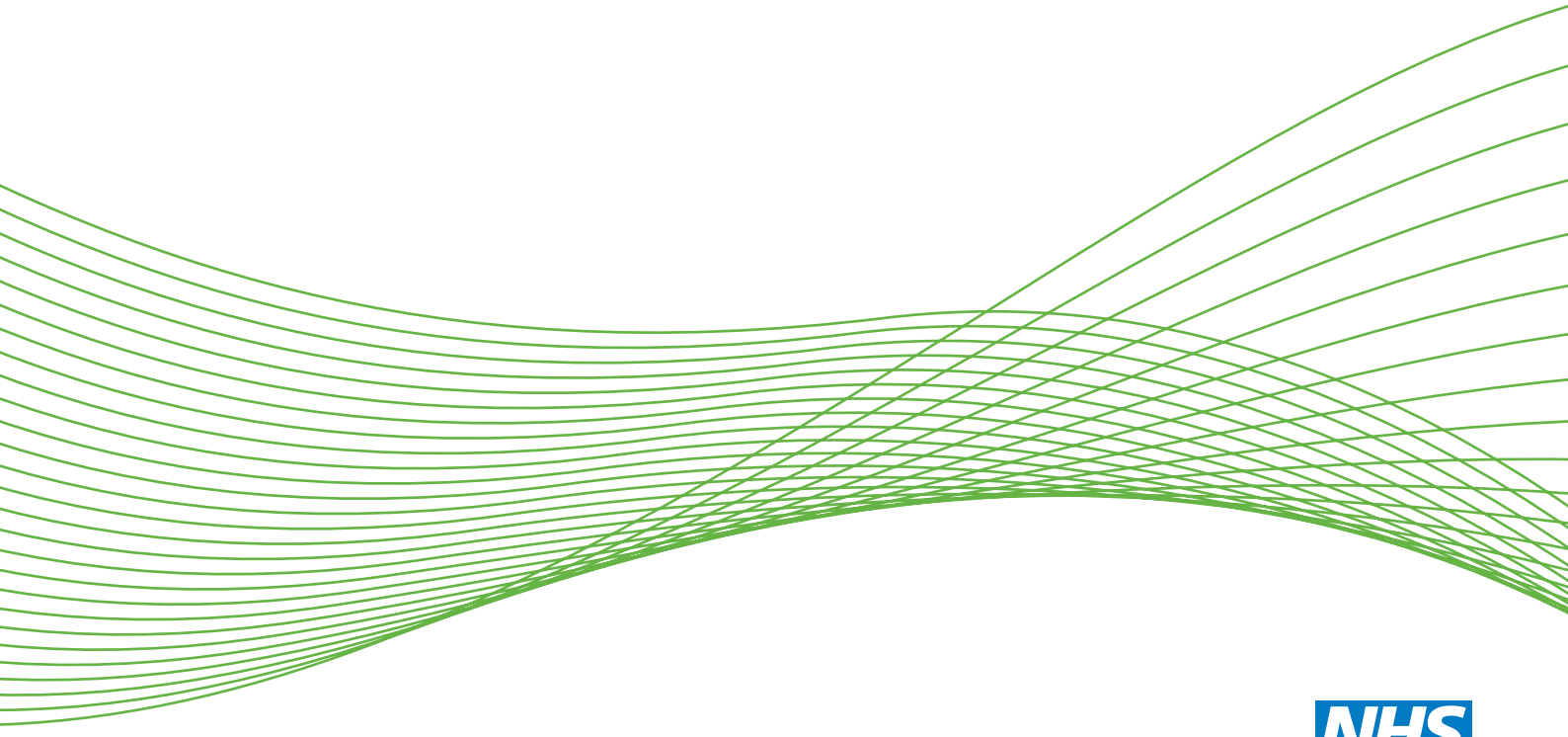

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Clinical effectiveness of interventions for treatment-resistant anxiety in older people: a systematic review

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Abstract

Clinical effectiveness of interventions for treatment-resistant anxiety in older people: a systematic review

Samantha Barton,[1*] Charlotta Karner,[1] Fatima Salih,[1] David S Baldwin[2] and Steven J Edwards[1]

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Background: Anxiety and related disorders include generalised anxiety disorder, obsessive–compulsive disorder, panic disorder, post-traumatic stress disorder and phobic disorders (intense fear of an object or situation). These disorders share the psychological and physical symptoms of anxiety, but each disorder has its own set of characteristic symptoms. Anxiety disorders can be difficult to recognise, particularly in older people (those aged over 65 years). Older people tend to be more reluctant to discuss mental health issues and there is the perception that older people are generally more worried than younger adults. It is estimated that between 3 and 14 out of every 100 older people have an anxiety disorder. Despite treatment, some people will continue to have symptoms of anxiety. People are generally considered to be 'resistant' or 'refractory' to treatment if they have an inadequate response or do not respond to their first treatment. Older adults with an anxiety disorder find it difficult to manage their day-to-day lives and are at an increased risk of comorbid depression, falls, physical and functional disability, and loneliness.

Objective: To evaluate the effectiveness of pharmacological, psychological and alternative therapies in older adults with an anxiety disorder who have not responded, or have responded inadequately, to treatment.

Data sources: Electronic databases (MEDLINE, MEDLINE In-Process and Other Non-Indexed citations, EMBASE, The Cochrane Library databases, PsycINFO and Web of Science) were searched from inception to September 2013. Bibliographies of relevant systematic reviews were hand-searched to identify additional potentially relevant studies. ClinicalTrials.gov was searched for ongoing and planned studies.

Review methods: A systematic review of the clinical effectiveness of treatments for treatment-resistant anxiety in older adults was carried out.

Results: No randomised controlled trial or prospective comparative observational study was identified meeting the prespecified inclusion criteria. Therefore, it was not possible to draw any conclusions on clinical effectiveness.

Limitations: As no study was identified in older adults, there is uncertainty as to which treatments are clinically effective for older adults with an anxiety disorder who have not responded to prior treatment. The comprehensive methods implemented to carry out this review are a key strength of the research presented. However, this review highlights the extreme lack of research in this area, identifying no comparative studies, which is a marked limitation.

Conclusions: Specific studies evaluating interventions in older adults with an anxiety disorder who have not responded to first-line treatment are needed to address the lack of evidence. The lack of evidence in this area means that older adults are perhaps receiving inappropriate treatment or are not receiving a particular treatment because there is limited evidence to support its use. At this time there is scope to develop guidance on service provision and, as a consequence, to advance the standard of care received by older adults with a treatment-resistant anxiety disorder in primary and secondary care. Evaluation of the relative clinical effectiveness and acceptability of pharmacological and psychological treatment in older adults with an anxiety disorder that has not responded to first-line treatment is key future research to inform decision-making of clinicians and patients. An important consideration would be the enrolment of older adults who would be representative of older adults in general, i.e. those with multiple comorbid physical and mental disorders who might require polypharmacy.

Study registration: The protocol for the systematic review is registered on PROSPERO (registration number CRD42013005612).

Funding: The National Institute for Health Research Health Technology Assessment programme.

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List of abbreviations

BNF	*British National Formulary*
CBT	cognitive–behavioural therapy
CG	clinical guideline
CI	confidence interval
CRD	Centre for Reviews and Dissemination
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
GABA	gamma-aminobutyric acid
GAD	generalised anxiety disorder
ICD	*International Classification of Diseases*
MeSH	medical subject headings
NICE	National Institute for Health and Care Excellence
OCD	obsessive–compulsive disorder
PTSD	post-traumatic stress disorder
QoL	quality of life
RCT	randomised controlled trial
SMD	standardised mean difference
SNRI	serotonin–noradrenaline reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
WHO	World Health Organization

Plain English summary

Anxiety and related disorders include generalised anxiety disorder, obsessive–compulsive disorder, panic disorder, post-traumatic stress disorder and phobic disorders (an intense fear of an object or situation). These disorders share psychological and physical symptoms of anxiety, but each disorder has its own set of characteristic symptoms. Most people with an anxiety disorder are diagnosed by the age of 40 years, but a few people will develop an anxiety disorder at older age (after the age of 65 years). Anxiety disorders can be difficult to recognise in older people, as there is the perception that older people are generally more worried than younger adults. In addition, older people are often reluctant to acknowledge that they are experiencing a mental health problem. It is estimated that the number of older people with an anxiety disorder is between 3 and 14 out of every 100 older people.

Treatments for anxiety include psychological therapies, pharmacological treatments and complementary therapies. Choosing a treatment for an older person with anxiety can be complicated. Older people typically have several medical conditions that need treatment and, because of the number of medications they are potentially taking, are at an increased risk of having side effects to potential treatments for anxiety. Some people will continue to feel anxious after initial treatment, which is known as treatment-resistant anxiety. In younger people, adding a second psychotropic drug to a first drug has been found to lower anxiety in some disorders. However, it is not known whether this treatment strategy is effective in older people.

At this time, there is little research on treatment-resistant anxiety in older people, and there is no resource that summarises the evidence for how effective the various therapies available are at treating treatment-resistant anxiety disorders in older people or how they compare against each other. This systematic review aimed to assess how well the treatments for treatment-resistant anxiety work in older people and how they compare with each other in improving the symptoms of anxiety. Other goals were to assess the adverse effects associated with the various treatments and to identify gaps in the evidence available. The project team searched the literature for evidence around the effectiveness of treatments and any side effects associated with them. No study assessing treatments for treatment-resistant anxiety in older adults was identified, underscoring the lack of research in this clinical area.

Scientific summary

Background

Anxiety disorders can affect people of all ages. In contrast to the appearance of anxiety that might be experienced during a stressful event, for example when taking a driving test, an anxiety disorder persists for a longer period of time and symptoms can progressively worsen if not treated. The onset of anxiety disorders is typically between childhood and young adulthood, with relatively few people (< 1%) developing an anxiety disorder for the first time after the age of 65 years. Recognition of the difficulties in differentiating symptoms of anxiety from physiological and physical changes (e.g. changes in sleep pattern) arising from the ageing process, together with the reluctance of many people to acknowledge psychological difficulties, has led to the realisation that anxiety in older people tends to be under-detected and under-treated. Many people with an anxiety disorder also suffer from various comorbidities, both physical and psychological, that can further complicate diagnosis and worsen the outcome of the disorder. Therefore, a comprehensive evaluation by an experienced clinician is needed. Disorders affecting physical health are common in older adults, and older adults often attribute symptoms of anxiety to their physical illness, which could result in non-diagnosis of their anxiety disorder.

The specific cause of symptoms in each anxiety disorder is not well established and the underlying aetiology of the disorders is yet to be fully elucidated. Treatments offered for an anxiety disorder are determined by the presumed underlying cause, though initial treatment might involve education and active monitoring. People whose symptoms of anxiety do not improve might subsequently be recommended to undergo psychological therapy or be prescribed a pharmacological treatment. Despite initial treatment, many people will continue to have symptoms of anxiety. Although there is no accepted definition of treatment resistance in anxiety disorders, people are generally considered to be resistant to treatment if they have made an inadequate response (either no response or only a partial response) or do not respond (refractory) to first-line treatment, irrespective of whether the first-line treatment was a psychological or pharmacological intervention.

As with younger adults, the course of anxiety disorders in older people is typically chronic or episodic in nature, and most disorders are unlikely to remit completely, even with long-term treatment. Compared with people of the same age and with what would be categorised as normal worries, older people with an anxiety disorder frequently experience greater difficulty in managing their day-to-day lives and are at an increased risk of comorbid depressive disorders, falls, physical and functional disability, and loneliness. Furthermore, the presence of an anxiety disorder is associated with reduced adherence with medical treatment, and long-term medical conditions are potentially exacerbated, which can result in a further loss of independence and increased reliance on family or carers. Anxiety has a considerable detrimental effect on quality of life (QoL) for both the older person with an anxiety disorder and that of any carers.

Objectives

The aim of the review was to evaluate the clinical effectiveness of medical, psychological and alternative therapies for treatment-resistant anxiety in older people.

Methods

A systematic review of the clinical effectiveness of treatments for treatment-resistant anxiety in older adults was carried out. Electronic databases (MEDLINE, MEDLINE In-Process and Other Non-Indexed citations, EMBASE, The Cochrane Library databases, PsycINFO and Web of Science) were searched from inception to September 2013. Bibliographies of relevant systematic reviews were hand-searched to identify additional potentially relevant studies. ClinicalTrials.gov was searched for ongoing and planned studies.

Studies eligible for inclusion in the review were randomised controlled trials (RCTs) and prospective comparative observational studies (matched control studies, case series and case–control studies) evaluating pharmacological, psychological and alternative therapies for treatment-resistant anxiety in older people. Study selection was carried out independently by two reviewers. Studies were eligible for inclusion in the review if they evaluated at least one intervention of interest, included only people aged ≥ 65 years or reported data for a subgroup of patients aged ≥ 65 years, compared the intervention with another intervention of interest and reported at least one of the following outcomes: reduction in symptoms of anxiety; response defined as proportion of people experiencing ≥ 50% reduction in symptom score from baseline); remission; functional disability; sleep quality; development of, or change in, symptoms of depression; adherence to treatment; QoL; carer outcomes; and adverse effects.

Summary of findings of included studies

No RCT or prospective comparative observational study was identified meeting the prespecified inclusion criteria. Therefore, it was not possible to draw conclusions on clinical effectiveness of interventions for treatment-resistant anxiety in older people.

Discussion

As no study was identified evaluating treatments in older adults, there is uncertainty as to which treatments are clinically effective for older adults with an anxiety disorder that has not responded to prior treatment. Older adults present with manifestations of anxiety different from those of younger adults. Taken together with the observation that response to treatment is often poorer in later life, it is probably inappropriate to extrapolate results of clinical effectiveness of interventions in anxiety disorders in younger adults to older adults.

Strengths and limitations

To our knowledge, the review reported here is the first systematic review of interventions for treatment-resistant anxiety in older adults. The comprehensive methods implemented to carry out the review are a key strength of the research presented. However, the review highlights the lack of research in this area, identifying no comparative studies, which is a limitation. Although multiple RCTs were identified that evaluated clinical effectiveness of interventions for treatment-resistant anxiety disorders, many limited inclusion to adults aged ≤ 65 years. Of those studies that included people ≥ 65 years, the mean ages reported at baseline suggest that most included people were much younger than 65 years. The potentially small number of people likely to be aged 65 years and over in the studies identified restricts the practicality and feasibility of carrying out a meta-analysis based on individual patient data. In addition, as the studies identified evaluated a range of treatments across various anxiety disorders, it is likely that the number of events for each treatment would be low, which would probably lead to considerable uncertainty in the results.

Conclusions

Studies evaluating interventions in older adults with an anxiety disorder that has not responded to first-line treatment are needed to address the lack of evidence in this area. This lack of evidence means that older adults are perhaps receiving inappropriate treatment, or are not receiving a particular treatment because there is no evidence to support its use. There is scope to develop guidance on service provision and, as a consequence, to advance the standard of care received by older adults with a treatment-resistant anxiety disorder in the primary and secondary settings.

Study registration

The protocol for the systematic review is registered on PROSPERO (registration number CRD42013005612).

Funding

The National Institute for Health Research Health Technology Assessment programme.

Chapter 1 Background

Description of health problem

Anxiety disorders can affect people of all ages. In contrast to the appearance of anxiety that might be experienced during a stressful event, for example when taking a driving test, an anxiety disorder persists for a longer period and symptoms can progressively worsen if not treated. Anxiety disorders can develop at any age, but onset typically occurs between childhood and young adulthood, with few people (< 1%) developing an anxiety disorder for the first time after the age of 65 years.[1] A US-based study (9282 English-speaking respondents aged ≥ 18 years) reported the median age at onset of anxiety disorders to be 11 years.[2] Although anxiety disorders among older people (≥ 65 years) are less common than in younger adults, it is acknowledged that the frequency in older adults is considerably higher than previously thought. Recognition of the difficulties in differentiating symptoms of anxiety from physiological and physical changes (e.g. changes in sleep pattern) arising from the ageing process, together with a common reluctance of older people to acknowledge psychological difficulties, has led to the realisation that anxiety in older people has been under-detected and under-treated.[1,3]

Many people with an anxiety disorder also have other medical conditions, both physical and psychological, that can further complicate diagnosis and worsen the long-term outcomes of the anxiety disorder. Of other anxiety and psychological disorders, depression is the most common comorbidity among younger and older adults.[1] Studies suggest that between 13%[4] and 23%[5] of people aged 55 years and older with a diagnosis of an anxiety disorder will also meet the criteria for a diagnosis of a major depressive disorder. One study in adults aged > 70 years found that 29.4% of those with an anxiety disorder had a comorbid depressive disorder.[6] In comparison, 20% of younger adults (aged 18–54 years) with a diagnosis of any anxiety disorder in the previous 6 months are likely to receive a simultaneous diagnosis of some type of mood disorder. Disorders affecting physical health are common in older adults, and older adults are more likely to attribute their symptoms of anxiety to their physical illness, which could result in non-diagnosis of their anxiety disorder.[1] Development of an anxiety disorder has been linked with thyroid problems (e.g. hypothyroidism or hyperthyroidism), respiratory and gastrointestinal conditions, arthritis, migraine headaches and allergic conditions.[7]

Treatments offered for an anxiety disorder are determined by the underlying cause of anxiety, though initial treatment might involve education and active monitoring. People whose symptoms of anxiety do not improve might subsequently be recommended to undergo psychological therapy or be prescribed a pharmacological treatment. Despite treatment, some people will continue to have symptoms of anxiety. With the exception of obsessive–compulsive disorder (OCD), there is no common definition as to what constitutes treatment resistance or treatment refractoriness in anxiety disorders.[8] People are generally considered to be resistant or refractory if they have an inadequate response (resistant) or do not respond (refractory) to first-line treatment, irrespective of whether the first-line treatment was a psychological or pharmacological intervention.

Diagnosis of an anxiety disorder

The term 'anxiety disorder' encompasses a broad range of conditions that manifest with symptoms of anxiety. Two major classification systems that can be used as a basis for differentiation between the different types of anxiety disorders are the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)[9,10]

and the World Health Organization's *International Classification of Diseases* (ICD).[11] Until 2013, the DSM identified 12 distinct anxiety disorders that could be captured within seven headings:[9]

- generalised anxiety disorder (GAD)
- OCD
- phobias, encompassing specific (simple) phobias and social phobia (also known as social anxiety disorder)
- stress disorders, including post-traumatic stress disorder (PTSD) and acute stress disorders
- panic disorder (with or without agoraphobia)
- anxiety disorders owing to known physical causes (e.g. medical conditions and symptoms caused by drug misuse)
- anxiety disorder not otherwise specified (covers symptoms not meeting the criteria for other anxiety disorders).

In 2013, the latest version of the DSM (version 5) was released.[10] Within the updated DSM, OCD is separated from the other anxiety disorders and is presented in a discrete chapter alongside related disorders. In addition, the stress disorders (PTSD and acute stress disorder) now lie within the chapter covering trauma- and stressor-related disorders. Separation anxiety disorder and selective mutism, which had previously been classified as 'Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence', were added to the anxiety disorders.[12] An accompanying comment on the revisions highlights that the changes underscore the discrete nature of the individual anxiety disorders, but that the sequential presentation of the chapters in the manual reflects the interconnectedness of the conditions.

The ICD-10 lists anxiety disorders under the general heading 'Neurotic, stress-related and somatoform disorders', which comprises the subgroups of:[11]

- phobic anxiety disorders (e.g. agoraphobia with or without panic disorder, social phobia and specific phobias)
- other anxiety disorders (e.g. panic disorder, GAD, and mixed anxiety and depressive disorder)
- OCD
- reaction to severe stress and adjustment disorders (acute stress reaction, PTSD and adjustment disorders)
- dissociative (conversion) disorders (e.g. dissociative amnesia and dissociative stupor)
- somatoform disorders (e.g. somatisation disorder and hypochondriacal disorders)
- other neurotic disorders (e.g. neurasthenia).

Diagnosis of an anxiety disorder can be challenging, particularly in older people. Symptoms of anxiety can be similar to those of other psychological conditions, such as depression, and the frequent presence of comorbid mental disorders further complicates diagnosis across all age groups.[13] Differentiating excessive anxiety from concerns around a recent distressing experience in older people, for example after a fall, can also prove difficult.[14] Anxiety in such scenarios might be expected by both the patient and the clinician and, therefore, the diagnosis of an anxiety disorder might not be considered. Additionally, some older people might have beliefs about emotional problems that make them reluctant to raise concerns about anxiety and it has also been recognised that older adults from ethnic minority groups often have different manifestations of anxiety. Both of these factors increase the difficulty in recognising anxiety in this age group.[13,15]

Compared with younger adults, older people often present to their clinician with non-specific symptoms, such as tiredness, or symptoms that are frequently related to the ageing process, such as a changing sleep pattern.[16] A common symptom of anxiety is deterioration in memory, which could be interpreted as signs of cognitive decline or onset of dementia.[17] Across all age groups anxiety disorders are often associated with pain and physical symptoms that could be a sign of heart disease or another physical illness[7] and, in these cases, identifying a presumed physiological cause is likely to be the focus of initial clinical investigations. Moreover, older people frequently require multiple concomitant treatments to manage

comorbid psychological and chronic medical conditions, and symptoms of anxiety could be thought to be associated with pharmacological treatment.

If an anxiety disorder is suspected, standardised screening questionnaires can initially be used to evaluate the presence and severity of anxiety. Validated screening tests include the Beck Anxiety Inventory, Spielberger State–Trait Anxiety Inventory, the Generalised Anxiety Disorder 7 (GAD-7) assessment and the Hospital Anxiety and Depression Scale.[18] The individual scales evaluate a set number of items to determine the severity of a patient's anxiety, with the number of items varying across the rating scales. The rating scales differ in that they were designed to assess anxiety in different patient groups; for example, the Beck Anxiety Inventory focuses on somatic symptoms of anxiety and was developed to differentiate between anxiety and depression. By contrast, the Hospital Anxiety and Depression Scale evaluates the presence of symptoms of anxiety and depression in physically ill people.[18] The effects of variation in language, education and culture across ethnic groups can lead to variation in judging the severity of patients' symptoms.[15] Although useful for initial evaluation and assessing treatment response, the generalised questionnaires are inadequate for determining which specific anxiety disorder is present. A formal clinical diagnostic assessment by an experienced clinician is required to categorise the disorder (based on criteria in the DSM-V or ICD-10).

Psychological and physical symptoms of anxiety are common across all anxiety disorders.[19] Some of the common psychological manifestations of anxiety include difficulty concentrating, feelings of trepidation, stress and restlessness, whereas common physical symptoms include fatigue, heart palpitations and trembling. In addition to the general symptoms, each anxiety disorder is associated with characteristic symptoms. Symptoms or triggers that can distinguish one disorder from another are listed in *Table 1*.[20] DSM-IV and ICD-10 criteria for the individual anxiety disorders are presented in *Appendix 1*.

Aetiology, pathology and prognosis

The specific cause of symptoms in each anxiety disorder is not well established and the underlying pathology of the disorders has yet to be fully elucidated. It is thought that a complex combination of genetic, environmental, psychological and developmental factors contribute to the development of an anxiety disorder.[21] Various factors have been found to increase the risk of developing an anxiety disorder, with some identified as specifically increasing this risk in older adults (summarised in *Box 1*).[1,19] Evidence indicates that susceptibility to anxiety disorders can be determined early in life. Early-life trauma has long been thought to increase the subsequent risk of developing a mental health illness.[21]

When a threat is perceived, various neurotransmitters and other chemical messengers, including circulating hormones, are released to modulate the neural circuitry involved in the generation of feelings of fear and anxiety.[22] The chief hormone involved in the autonomic nervous system is the catecholamine 'adrenaline' (also known as epinephrine), produced by the adrenal glands. Adrenaline triggers a physical response to stress, including increased heart rate and breathing rate.[22] At the same time another hormonal system,

TABLE 1 Symptoms and triggers associated with individual anxiety disorders[20]

Anxiety disorder	Disorder-specific symptoms
GAD	Constant worries and fears
OCD	Unwanted persistent or repetitive thoughts or behaviours that seem impossible to stop or control
Social phobia	A debilitating fear of being seen negatively by others and humiliated in public
Specific phobia	Excessive or irrational fear of a specific object or situation
PTSD	Extreme anxiety disorder that can occur in the aftermath of a traumatic or life-threatening event
Panic disorder	Repeated, unexpected panic attacks as well as fear of experiencing another episode

BOX 1 Risk factors for developing an anxiety disorder

Risk factors for general population[19]

- Being female.
- Traumatic experience in either childhood or adulthood.
- Physical illness (e.g. thyroid problems and chronic medical conditions).
- Stress over a prolonged period of time (e.g. ongoing concern about finances).
- Genetic predisposition.
- Drug or alcohol abuse.

Risk factors for older adults[1]

- Being female.
- Having multiple chronic medical conditions (particularly chronic obstructive pulmonary disease, cardiovascular disease, thyroid disease and diabetes).
- Being single, divorced or separated.
- Lower level of education.
- Perceived (self-reported) poor health.
- Sleep disturbance.
- Effects of medications (e.g. corticosteroids, antidepressants, stimulants and bronchodilators).
- Alcohol or prescription medication misuse or abuse.
- Physical limitations in daily activities.
- Stressful life events.
- Adverse events in childhood.
- Neuroticism or preoccupation with somatic (physical) symptoms.

the hypothalamo–pituitary–adrenal axis, initiates a pathway involving several hormones and other messengers. The culmination of the various signalling interactions is the release of adrenal hormones, called glucocorticoids, of which cortisol is the most important.[22,23] Cortisol causes a rapid release of the body's energy stores to maintain blood sugar levels and also suppresses any immune response. Dysregulation of the hypothalamo–pituitary–adrenal axis is known to be associated with an increased risk of development of major depression.[24] Furthermore, the ageing brain is less able to downregulate the hypothalamo–pituitary–adrenal axis and is more susceptible to physiological stressors.[25] Thus, in older adults chronic anxiety can cause hyperactivity of this system, which can detrimentally affect memory and executive function.

The main neurotransmitters implicated in anxiety disorders are noradrenaline, serotonin, dopamine and gamma-aminobutyric acid (GABA).[26] The discovery that anxiolytic (anti-anxiety) drugs interact with neurotransmitters led to the proposal that abnormal activity in the brain is a physiological characteristic of anxiety.[21]

Imaging of brain activity during exposure to triggers of anxiety has suggested that the amygdala and the hippocampus have an integral role in eliciting feelings of fear and anxiety.[21,26] The amygdala is located deep in the anterior medial section of each temporal lobe and is thought to be involved in memory storage and communication.[27] It is thought that the amygdala facilitates signal transfer between the components of the brain that process incoming sensory signals and those that interpret the signals. An imbalance of the signalling pathway, possibly resulting from overactivity of the amygdala, is thought to contribute to excessive anxiety.[27] The amygdala functions as a warning system, alerting for potential impending threat and activating the nervous system to generate feelings of fear or anxiety. The central part of the amygdala is thought to store emotional memories and, thus, could have a role in the development of a specific phobia.

Located in the forebrain and forming part of the limbic system, which is the area of the brain that responds to stress, the hippocampus is important in spatial navigation and the formation of memories.[21] The hippocampus is involved in consolidating a life-threatening or traumatic event into a memory. Some studies suggested that the hippocampus is smaller in some people who have PTSD, with the change in size[28–31] thought to be induced by sustained exposure to cortisol, which is known to damage the hippocampus[23] during a prolonged period of stress.[32] However, recent research involving identical (monozygotic) twins suggests that reduced hippocampal volume is predetermined and volume is linked with susceptibility to PTSD.[33] Other studies in identical or non-identical (dizygotic) twins have found that all the anxiety disorders have a moderately strong genetic basis, accounting for 30–40% of the probability of a person developing an anxiety disorder.[34,35]

The extent to which environmental factors determine the risk of developing an anxiety disorder is not established. However, one environmental factor known to be linked with the risk of a person developing an anxiety disorder is the childhood relationship with parents.[36,37] Positive parenting experiences are important to provide children with a feeling of security. Family conflict, lack of structure and discipline, and overprotection, amongst others, have been identified as parental experiences that predispose a person to developing an anxiety disorder, either during childhood or in later life.[37]

Categorisation of treatment resistance in anxiety disorders is complex. It has been recommended that the assessment of remission and recovery in anxiety disorders includes an assessment of functional status.[38] Recognition of treatment resistance is further complicated by the frequent presence of symptoms of more than one anxiety disorder and the presence of a comorbid disorder that potentially disrupts treatment. Response to treatment or, conversely, non-response to treatment in anxiety disorders has been investigated in various studies.[38] Factors thought to contribute to poor response to treatment have been divided into four categories (outlined in *Box 2*): pathology, environment, patient and clinician. Difficulty in diagnosing treatment resistance is affected by the same problems encountered when diagnosing an anxiety disorder, including changes in, and variation across, criteria used to categorise anxiety disorders, under-recognition of the disorder and use of clinically inadequate doses of pharmacological agents in initial treatment.

As with younger adults, the course of established anxiety disorders in older people is typically chronic or episodic in nature, and most disorders are unlikely to remit completely, even with long-term treatment.[39] One US-based study evaluating people with GAD (164 people) reported a mean age at onset of an anxiety disorder of 21 years and an average duration of illness of about 20 years.[40] Studies suggest that anxiety disorders are more chronic than other common mental disorders and that comorbid depression and anxiety has a worse prognosis.[41] The presence of an anxiety disorder has been identified as an independent risk factor for subsequent onset of suicidal ideation and attempts.[42] In all age groups, the frequent comorbidity of anxiety disorders, depression, and alcohol and drug misuse complicates the evaluation of long-term prognosis. In clinical trials involving a mixed-age population and different anxiety disorders, remission rates of 20–47% have been reported.[43] The study evaluating people with GAD found that, despite treatment, only 25% of patients achieved symptomatic remission from GAD at 3 years,[40] with a risk of relapse over the subsequent year of about 15%; risk of relapse for those achieving partial symptomatic remission increased to 30%.[40]

Incidence and prevalence

Data reported on prevalence and incidence vary across studies. This disparity can be attributed to different methodological procedures used, including sampling, with some studies using nationally representative samples and others using convenience samples; differences in the tools used to diagnose an anxiety disorder; and differences in the anxiety disorders included in the evaluation.[1]

The prevalence of anxiety disorders in older people exceeds that of late-life depression and cognitive dysfunction,[44] with estimated rates of anxiety disorders ranging from 3.2% to 14.2% in people aged over 65 years.[1] In England during 2007, 2.28 million people were estimated to have an anxiety disorder, with 13% of those being aged over 65 years.[45] The prevalence of anxiety disorders is even higher among older

BOX 2 Factors thought to be involved in poor response to treatment in anxiety disorders

Pathology related

- Exact underlying pathophysiology is unknown.
- Multiple neurotransmitters participation and interaction.
- Complex receptor and feedback structure of every single transmitter system.
- Diagnosis – dimension approach.
- Genetics of the disorders overlap and unclear what is inherited.
- Current biological treatments are empirical and have limitations.
- Cognitive–behavioural theory is disconnected from biological substrate.

Environment related

- Severe stressors.
- Childhood stressors.
- Long-term persistent stressors.
- Life cycles.

Patient related

- Severity.
- Medical comorbidity.
- Psychiatric comorbidity.
- Non-compliance.
- Cultural factors.

Clinician related

- Lack of knowledge in primary care.
- Cognitive–behavioural theory is disconnected from biological substrate.
- Cost leading to limited doctor–patient relationship.

people who are housebound and require home care, those who live in residential care facilities (e.g. a nursing home or assisted living) and those who have a chronic medical illness. In addition, 15–20% of older people experience symptoms of anxiety that, although debilitating, do not meet criteria for a psychiatric diagnosis.[3] Most people with a primary anxiety disorder experienced the onset of the condition before the age of 41 years (90%), with 75% of people diagnosed with an anxiety disorder before the age of 21 years.[46]

A UK-based epidemiological survey of common mental disorders [including depression, GAD, panic disorder, phobias (in general) and OCD] reported GAD to be the most common anxiety disorder affecting people in the UK, with a prevalence of 4.4%. The prevalence of PTSD was 3.0%, and only a small proportion of people (< 1.5%) met diagnostic criteria for the remaining disorders.[47] A review of the literature on prevalence of anxiety disorders in older people identified considerable variation in prevalence of the individual disorders (summarised in *Table 2*).[1] The results reported in the review suggest that estimates of prevalence are highest for social phobia (with or without agoraphobia) and GAD. However, elsewhere, it has been reported that GAD is the most common anxiety disorder affecting older adults, with a prevalence of 3.1–11.2%.[3] The authors of this comprehensive review note that, because of methodological issues identified earlier, it is not possible to draw definitive conclusions on prevalence.[3] Data on prevalence of treatment-resistant anxiety in older people were not identified.

TABLE 2 Estimated prevalence of anxiety disorders in older people[1]

Anxiety disorder	Prevalence in older people
GAD	1.2–7.3%
OCD	0.1–0.8%
Social phobia	3.1–10.2%
Specific phobia	Not reported
PTSD	0.4–1.0%
Panic disorder	0.1–1.0%

Impact of health problem

When comparing older people with an anxiety disorder with people of the same age with what would be categorised as 'normal' worries, older people with an anxiety disorder frequently experience greater difficulty in managing their day-to-day lives and are at an increased risk of comorbid depressive disorders, falls, physical and functional disability, and loneliness.[1,3] Furthermore, the presence of an anxiety disorder is associated with reduced compliance with medical treatment and potential exacerbation of chronic conditions, which can result in loss of independence and increased reliance on family or carers. Anxiety has a considerable detrimental effect on the quality of life (QoL) of both the older person with an anxiety disorder and their carers.

Significance for the NHS

As a result of changing demographics, it is estimated that the number of people with an anxiety disorder in England will grow to 2.56 million by 2026, with the largest increases observed in older age groups.[45] Compared with data from 2007, it has been predicted that the number of people aged 85 years and older with an anxiety disorder in England will increase by 66% by 2026.[45] Anxiety disorders in older adults will become a source of increasing personal and societal cost.

Current service provision

The National Institute for Health and Care Excellence (NICE) has produced clinical guidelines (CGs) on the management of GAD and panic disorder [with or without agoraphobia; (CG113)],[48] PTSD (CG26),[49] OCD (CG31)[50] and social anxiety disorder (CG159).[51] Of the guidelines available, CG113 addresses interventions for treatment-resistant GAD and CG31 outlines management of OCD that is not responding to treatment, but neither guideline outlines management of inadequate response to treatment specifically in older adults. Guidance from NICE advocates a stepped care pathway for GAD,[52] panic disorder[53] and OCD,[54] as depicted in NICE clinical pathways. By contrast, the pathways for PTSD[55] and social anxiety disorder[56] are not based on a series of set treatment phases.

Although treatment strategies are tailored to treat the particular symptoms associated with the needs of the patient with an anxiety disorder, fundamentally the core principles of the clinical pathways for recognition and treatment of panic disorders are similar,[52–56] with initial steps involving the identification and assessment of severity of the anxiety disorder. Providing patients with information to understand their disorder, and the treatment options available, are proposed as an important components of treatment across anxiety disorders. Evidence from a systematic review indicates that self-help is more effective than waiting list control in the treatment of anxiety, with a significant reduction in symptoms of anxiety [standardised mean difference (SMD) −0.86, 95% confidence interval (CI) −1.03 to −0.69 (20 studies, $n = 1121$)].[57] It should be noted that the evidence in this review is based on a synthesis of data from trials in various anxiety disorders and moderate statistical heterogeneity (44%) was present.[57] Considered separately, the evidence base for the effectiveness of self-help in the individual anxiety disorders is limited.

Self-help, either guided or non-guided, is described in CG113 as a low-intensity psychological treatment for GAD – these low-intensity psychological interventions listed in CG113 are summarised in *Table 3*.[48] Definition of what constitutes low-intensity psychological therapies varies across studies, but such interventions are generally those with little or no involvement of a therapist.[58] Examples include bibliotherapy and computer-guided interventions. As contact with a health-care professional is minimal, low-intensity psychological interventions increase access to psychological treatments for people experiencing mild to moderate anxiety and depressive disorders.[48] Increasing access to psychological interventions for the treatment of anxiety disorders and depression is a key tenet of the Improving Access to Psychological Therapies programme, which was launched in the UK in October 2007.[59]

In GAD, if symptoms of anxiety persist after low-intensity psychological interventions NICE recommends offering high-intensity psychological interventions as a treatment option.[48] People with anxiety disorders and depression frequently prefer to try psychological interventions before pharmacological agents. Compared with low-intensity therapies, high-intensity interventions are typically more resource intensive, involving more contact with appropriately trained health-care professionals; examples of high-intensity psychological interventions include cognitive–behavioural therapy (CBT) and applied relaxation (see *Table 4*). Alternatively, people may be offered a pharmacological treatment if they prefer, with a selective serotonin reuptake inhibitor (SSRI) typically the first choice for treatment.[48] For OCD that is associated with moderate functional impairment, NICE recommends offering a choice between higher-intensity CBT or a course of a SSRI as initial treatment.[50] Other pharmacological options for anxiety disorders include a serotonin–noradrenaline reuptake inhibitor (SNRI), pregabalin or a benzodiazepine. Benzodiazepines have been associated with toxicity, dependence, abuse and cognitive impairment, and are not recommended for the long-term treatment of anxiety.[60]

Patients who do not respond to initial psychological or pharmacological treatment, those who are at high risk of self-harm or neglect, and those suffering from substantial comorbidities might require complex drug and/or psychological treatment, crisis services, day hospitals or inpatient care.[48,50]

Guidance on the treatment of anxiety and treatment-resistant anxiety in older adults is lacking. It is well recognised that anxiety in older people manifests differently from anxiety in younger people. Older people

TABLE 3 Low-intensity interventions for GAD described in NICE CG113[48]

Intervention	Description
Non-facilitated self-help	Self-administered intervention intended involving a self-help resource (usually a book or workbook)
	Similar to guided self-help, but with minimal therapist contact (infrequent telephone call lasting no longer than 5 minutes)
Guided self-help	Self-administered intervention intended to treat symptoms of anxiety
	Typically involves a CBT-based self-help resource (e.g. leaflets, books, self-help workbook or multimedia)
	Limited support from a health-care professional: contact between the person and the health-care professional ranges from 3 to 10 sessions, totalling 3–6 hours of therapy delivered either face to face or by telephone
Psychoeducational group	Psychoeducation delivered to a large group (typically 20–24 people)
	Focuses on educating people about the nature of anxiety and ways of managing anxiety using cognitive–behavioural techniques
	Weekly sessions led by appropriately trained practitioners (one therapist to 12 group members) and involving presentations and self-help materials
	Sessions typically last for 2 hours and take place over a 6-week period

CBT, cognitive–behavioural therapy.

are more likely to consult their doctor because of somatic (i.e. physical) or general symptoms (e.g. change in sleep pattern) rather than concerns about their anxiety.[16] As a result, in primary care, older adults are more likely to be prescribed a benzodiazepine than a SSRI; benzodiazepines are most frequently used to manage insomnia, particularly in older adults in whom insomnia is caused by anxiety or depression. The main adverse effects associated with benzodiazepines are sleepiness, unsteadiness and difficulty with memory and concentration; all of which are more severe in older adults. Benzodiazepines are also associated with a considerable increase in the risk of falls for an older person.[61]

Optimising treatment to manage anxiety disorders in older people is complex, and treatment typically involves a combination of psychotherapy, pharmacotherapy and complementary therapies. Older people frequently require multiple concomitant treatments to manage comorbid psychological and chronic medical conditions,[1] and are at risk of under-treatment as physicians take care to restrict the number of medications prescribed. Physiological changes that occur during ageing lead to decreased metabolism and reduced clearance of pharmacological agents. As a result, older people are at an increased risk of adverse effects from treatment, a risk that is compounded by increasing the number of drugs administered.[62] Additionally, it is well recognised that adherence to treatment among older people can be lower than among younger adults.[1] Lower tolerability for treatment and decline in cognitive function, which is a natural part of ageing, both contribute to the lower rate of compliance.[62] Poor compliance can exacerbate chronic medical conditions, lead to increased reliance on carers and, ultimately, result in admission to a residential facility.

Alternative treatment strategies with potential for use in treatment-resistant anxiety include switching medication and combining pharmacotherapy and psychotherapy, but there is limited evidence evaluating these treatments. One strategy for which there is a strong evidence base in treating resistant anxiety in a mixed-age population is augmentation of pharmacotherapy with a second agent. In a review of the literature, Ipser *et al.*[63] identified 28 randomised controlled trials (RCTs) evaluating the addition of primarily antipsychotic drugs (17 RCTs) to ongoing pharmacotherapy. Most RCTs evaluated short-term (average follow-up of 7 weeks) augmentation of a SSRI with an antipsychotic for the treatment of people not responding to first-line treatment for OCD. Although the findings suggest that this augmentation approach can be effective in the short term, methodological and clinical heterogeneity among trials preclude drawing definitive conclusions on effectiveness. Treatment of older people is typically complicated by issues such as polypharmacy and comorbidity. Physiological functions change with age; for example, the way in which the body metabolises a drug could differ greatly in older adults compared with younger adults and, for these reasons, it might be considered inappropriate to extrapolate results from trials involving a mixed-age sample to older adults. Moreover, because of the additional complexity of treatment, clinicians in the primary care setting are likely to be cautious about prescribing psychotropic treatments for older people.

Description of technology under assessment

The interventions under assessment are those that would be used to treat symptoms of anxiety that had not responded to prior treatment, which, based on NICE guideline CG113 for GAD, would comprise offering people the choice of either high-intensity psychological treatments or a drug treatment and, in refractory cases, a combination of psychological and pharmacological treatments;[48] guidance on treatment of persistent anxiety in older people is not available. In the case of GAD that has not responded to low-intensity psychological interventions, NICE recommends basing choice of treatment on patient preference as there is no evidence that one mode of treatment (i.e. psychological vs. pharmacological) is clinically more effective than the other. Based on clinical expert opinion and recommendations for escalation of treatment in CG113,[48] for the review reported here, treatment resistance/refractoriness was defined as no substantial improvement in symptoms of anxiety, despite treatment with an intervention for which there is evidence of clinical effectiveness in the treatment of an anxiety disorder.

High-intensity psychological treatments

High-intensity psychological treatments typically involve one-to-one therapy with a mental health professional and take place over multiple treatment sessions. High-intensity psychological techniques are complex and considerably more resource intensive than low-intensity psychological interventions, comprising multiple components that are typically adapted to an individual; an overview of components of some high-intensity psychological therapies is presented in *Table 4*.

Cognitive–behavioural therapy is widely employed in the treatment of anxiety and depression, either on a one-to-one basis or delivered as part of a group session (see *Table 4*). CBT has been found to be clinically beneficial in treating anxiety symptoms associated with GAD,[64] panic disorder,[65] PTSD,[66] social anxiety disorder[67] and OCD.[68] Other forms of psychological intervention have been found to offer more benefit in some disorders than in others. For example, applied relaxation is an alternative to CBT that has benefit in the treatment of GAD[64] and panic disorder[65] (see *Table 4*), and trauma-focused CBT as well as eye movement desensitisation and reprocessing are used in the treatment of anxiety associated with PTSD[49,66] (*Table 4*). Exposure and response prevention techniques are used in OCD,[68] panic disorder[65] and social anxiety disorder.[67]

Despite evidence that psychological interventions can be effective, older adults generally have reduced access to such services compared with younger adults. In 2007, it was estimated that 51% of people with an anxiety disorder in England were not in contact with health-care services and, of those who were in contact, 46% were not receiving pharmacological or psychological therapy.[45] Information focusing on older adults was not identified. A report from the Older People's Psychological Therapies Working Group in Scotland identified that fewer than 10% of older people with depression are referred to specialist mental health services, compared with 50% of younger adults.[69] Moreover, the survey also identified that 80% of older people with depression were not receiving any treatment. A lack of available services was identified as the largest barrier to older adults receiving high-intensity psychological interventions. The effectiveness of psychological interventions in older adults with treatment-resistant anxiety is unknown.

Pharmacological treatments

For OCD, social anxiety disorder, GAD and panic disorder, NICE guidance recommends offering a SSRI, in particular sertraline, as the first pharmacological treatment.[48,50,51] Although sertraline is not licensed for the treatment of GAD, NICE acknowledges that sertraline is clinically effective in treating anxiety disorders and appears to be the most cost-effective of the SSRIs.[48] Alternative pharmacological agents used to treat symptoms of anxiety are SNRIs, tricyclic antidepressants (TCAs), benzodiazepines (e.g. diazepam), some anticonvulsants [e.g. pregabalin (Lyrica®, Pfizer)], beta-blockers and other agents with an anxiolytic effect (e.g. buspirone).[70] In addition, augmentation of ongoing pharmacotherapy with an antipsychotic agent has been found to be clinically effective at improving symptoms of anxiety in treatment-resistant anxiety disorders.[63] However, the effectiveness of these agents in treatment-resistant older adults has not been evaluated. First-line pharmacological treatment is most likely to be prescribed by a primary care physician.

Clinical trials frequently exclude older adults, and thus there is limited information available on treatment response in this population.[62] Polypharmacy, age-related changes in physiological processes and increased risk of adverse events, including falls, confusion and depression, present challenges to prescribing pharmacological agents for older adults. Determination of the appropriate dose for older adults can also be troublesome. Age-related changes in physiology could lead to increased volume of distribution of the drug or decreased drug clearance, both of which may result in increased plasma drug concentrations and adverse effects.[62]

Selective reuptake inhibitors

Selective serotonin reuptake inhibitors act by selectively inhibiting the reuptake of serotonin (5-hydroxytryptamine) and SNRIs act by selectively inhibiting the reuptake of noradrenaline and serotonin, both of which are neurotransmitters. Serotonin is involved in the regulation of mood, sleep and appetite, and noradrenaline has a role in the body's response to stress. Dysfunction of the biological pathways

TABLE 4 High-intensity interventions for anxiety disorders[48,49]

Intervention	Description
CBT	Psychotherapeutic approach encompassing various techniques based on cognitive–behavioural models of disorders. Working with the person with the disorder, the therapist designs specific techniques that target dysfunctional emotions and cognitive processes. Treatment goals might include recognising the impact of behavioural and/or thinking patterns on feeling states and encouraging alternative cognitive and/or behavioural coping skills
Applied relaxation	Focuses on applying muscular relaxation at times of anxiety and facilitates early response to feelings of anxiety. Applied relaxation is carried out by practitioners of CBT and sessions are typically weekly, lasting for 12–15 weeks. Components of applied relaxation include: • progressive muscle relaxation (focus on particular muscle groups and recognition of the difference between tensing and relaxing of muscles) • release-only relaxation (allows the person to enter directly a relaxed state) • cue-controlled relaxation [reduces the time needed to relax (2–3 minutes) by generating an association between a cue word and muscle relaxation] • rapid relaxation (further reduces the time needed to relax by selecting specific cues that are encountered regularly and practised regularly throughout the day until a state of deep relaxation can be reached in less than 30 seconds) • applied relaxation (application of relaxation skills acquired through exposure to anxiety-provoking situations)
Psychodynamic therapy	Focuses on unconscious processes as manifested in a person's present behaviour • non-directive treatment with the goals of increasing self-awareness and understanding of the influence of the past on present behaviour • process examines unresolved conflicts and symptoms originating from past conflicts, with a technical focus on interpreting and working though the dysfunctional situation
Non-directive therapies	Psychotherapeutic approach in the person is helped to identify conflicts and to clarify and understand feelings and values, during which the practitioner does not proffer advice or interpretation
Trauma-focused CBT	Focuses memories, thoughts and feelings that a person has about the traumatic event
Eye movement desensitisation and reprocessing	Focuses on memories of the traumatic event (including negative thoughts, feelings and sensations experienced at the time of the event) with the goal of generating more positive emotions, thoughts and behaviour: • person focuses on an image connected to the traumatic event and the related negative emotions, sensations and thoughts, while concentrating on an object (typically the therapist's fingers moving from side to side in front of the eyes) • after each set of eye movements (about 20 seconds), person is encouraged to discuss the images and emotions experienced during the eye movements • process is repeated, with a focus on difficult, persisting memories, with encouragement to have a positive thought about the event
Exposure and response prevention	Goal is habituation and extinction of responses • person generates a list of objects/situations that they fear, or avoid, and ranks in order of decreasing fear (most feared at the top) • person tackles the object that triggers their anxiety, starting with the least feared object/situation and working up to the most feared • repeated daily for > 1 week

involving serotonin and noradrenaline has long been thought to have a role in the pathogenesis of anxiety and depression.[71] It is thought that SSRIs and SNRIs alleviate symptoms of anxiety and depression by blocking reuptake and, thus, increasing the levels of serotonin and noradrenaline available. Various SSRIs and SNRIs have been recommended for the treatment of individual different anxiety disorders;[70] anxiety disorders listed by indication for SSRIs or SNRIs as specified in the *British National Formulary* (BNF) are presented in *Table 5*. Oral doses for the individual SSRIs and SNRIs reported in the BNF are presented in *Appendix 2*.

Selective serotonin reuptake inhibitors are the first choice of pharmacological treatment for anxiety disorders and major depression because they have a better tolerability and adverse effect profile than other classes of antidepressants.[72] In particular, compared with TCAs, the SSRIs do not cause cardiac conduction abnormalities in overdose and have a low propensity to cause seizures. There are differences in the adverse effect profiles of the SSRIs, but frequently reported adverse effects include gastrointestinal disturbances (nausea, vomiting, abdominal pain, diarrhoea and constipation), dry mouth, drowsiness, insomnia, weight gain and sexual dysfunction.

Caution when prescribing SSRIs is advised for people with epilepsy, cardiac disease, diabetes mellitus, acute angle-closure glaucoma or those with a history of mania. In addition, caution should be used when a person has active, or a history of, gastrointestinal bleeding, or is already taking a drug that is associated with an increased risk of bleeding.[60]

Benzodiazepines

Benzodiazepines act by enhancing the effect of the neurotransmitter GABA at the $GABA_A$ receptor complex. By increasing the effects of GABA, benzodiazepines induce sedative, hypnotic (sleep-inducing), anxiolytic, anticonvulsant and muscle-relaxing effects.[60] Most benzodiazepines are given orally, but they can also be administered intravenously, intramuscularly or rectally.[60] Examples of benzodiazepines used as anxiolytics include diazepam, alprazolam, chlordiazepoxide hydrochloride, lorazepam (Ativan®, Valeant) and oxazepam.

Prescription of benzodiazepines is widespread, but evidence of dependence (physical and psychological) and tolerance has restricted their usability.[60] Benzodiazepines can be effective in alleviating the acute

TABLE 5 Selective reuptake inhibitors used for the treatment of anxiety disorders as specified in the BNF[60]

Drug	Indication					
	GAD	OCD	Social anxiety disorder	Specific phobia	PTSD	Panic disorder
SSRIs						
Escitalopram (Cipralex®, Lundbeck)	✓	✓	✓	–	–	✓
Sertraline (Lustral®, Pfizer)	–	✓	✓	–	✓	✓
Paroxetine (Seroxat®, GlaxoSmithKline)	✓	✓	✓	–	✓	✓
Citalopram (Cipramil®, Lundbeck)	–	–	–	–	–	✓
Fluoxetine (Prozac®, Eli Lilly)	–	✓	–	–	–	–
Fluvoxamine (Faverin®, Abbott Healthcare)	–	✓	–	–	–	–
SNRIs						
Venlafaxine (Efexor® XL, Pfizer)	✓	–	✓	–	–	–
Duloxetine (Cymbalta®, Eli Lilly)	✓	–	–	–	–	–

symptoms of severe anxiety in the short term (2–4 weeks), but their use for mild anxiety or chronic conditions is generally not recommended. In addition, because older adults are at an increased risk of ataxia and confusion (which in turn increases risk of falling), use of benzodiazepines in older adults is not recommended. Older adults with an anxiety disorder are most likely to consult their general practitioner and, in this setting, might be inappropriately prescribed a benzodiazepine as an initial treatment.[73] Analysis of patient records from 131 UK general practices (including approximately 162,000 registered patients annually aged ≥ 65 years) found that in 2003, benzodiazepines (52.4/1000 people) were one of the most frequently prescribed potentially inappropriate drugs.[73]

Tricyclic antidepressants

Originally developed in the 1950s and 1960s, TCAs act by inhibiting the reuptake of serotonin, noradrenaline and dopamine[72] and include drugs such as amitriptyline, clomipramine hydrochloride and dosulepin hydrochloride.[60] Some TCAs inhibit reuptake of serotonin to a greater extent, whereas others may predominantly block reuptake of noradrenaline. However, most TCAs inhibit reuptake of both serotonin and noradrenaline. Unlike the SSRIs, the TCAs are non-selective and also interact with additional receptors and channels, including histamine, cholinergic, adrenergic and dopamine receptors.[74] Although the TCAs are clinically effective in treating anxiety and depression, their interaction with receptors that are unrelated to depression can lead to the development of often intolerable adverse effects, the most severe of which involve the cardiovascular system.[74] The adverse effect profile of TCAs limits their clinical use. The BNF lists clomipramine for use in phobic and obsessional states at an initial dose of 25 mg daily for younger adults, and an initial dose of 10 mg daily in older adults.[60] The dose can be increased over 2 weeks to 100–150 mg daily to a maximum of 250 mg daily. Older adults are particularly susceptible to the adverse effects associated with TCAs. A systematic review on the risk of adverse effects associated with antidepressant use in older adults identified a statistically significant increase in the risk of falls and of fractures with use of TCAs.[75] Initially a low dose should be used and patients should be monitored closely, particularly checking for psychiatric and cardiac adverse effects.[60]

Tricyclic antidepressants and related antidepressants should be used with caution in people with cardiovascular disease, epilepsy, diabetes, and, because of the increased risk of arrhythmias, in people with concomitant conditions such as hyperthyroidism and phaeochromocytoma.[60] The antagonistic action of TCAs at muscarinic acetylcholine receptors means that caution is also needed when treating people with prostatic hypertrophy, chronic constipation, increased intraocular pressure or urinary retention or those with a susceptibility to angle-closure glaucoma. TCAs should be used with caution in people at high risk of suicide or with a history of psychosis or bipolar disorder; for people with bipolar disorder, treatment with a TCA should be stopped if the person enters a manic phase.

Antipsychotics

Antipsychotics are used to treat disorders involving psychosis (with symptoms such as delusions and hallucinations), including schizophrenia and bipolar mania.[76] However, the effectiveness of antipsychotics is not limited to treating psychosis, with evidence of benefit in mood and anxiety disorders, particularly when used as an adjunctive therapy. Antipsychotics have historically been categorised as first-generation (also known as typical or conventional) or second-generation (also known as 'atypical') antipsychotics, based on when they were developed;[76] examples from the classes listed in the BNF are given in *Table 6*.[60] It is recommended that use of antipsychotics should be limited to the treatment of severe anxiety symptoms and that they should be used only for short-term treatment.

The first-generation antipsychotics were developed in the 1950s, with second-generation antipsychotics emerging in the 1980s.[76] First- and second-generation antipsychotics both act by blocking dopamine receptors, but second-generation antipsychotics do so to a lesser extent. Second-generation antipsychotics also interact with receptors for neurotransmitters other than dopamine, including serotonin and histamine, and the variation in targeted receptors results in markedly different clinical and adverse effect profiles within the group.[76,77] Choice of treatment is typically determined by medication history and individual risk of particular side effects, such as weight gain or impaired glucose tolerance. Antipsychotics can be given

TABLE 6 Examples of antipsychotics used as an adjunctive treatment in the management of severe anxiety[60]

Antipsychotic	Usual daily dose for short-term use in management of severe anxiety
First-generation antipsychotics	
Chlorpromazine	75–300 mg
Haloperidol	500 µg twice daily
Pericyazine	15–30 mg divided into two doses
Perphenazine	12 mg
Prochlorperazine	15–20 mg in divided doses
Trifluoperazine	2–4 mg in divided doses
Second-generation antipsychotics[a]	
Amisulpride	50–800 mg
Aripiprazole (Abilify®, Otsuka and Bristol-Myers Squibb)	10–30 mg
Clozapine (Clozaril® and FazaClo®, Novartis Pharmaceuticals)	200–450 mg
Olanzapine	10–20 mg
Paliperidone (Invenga®, Janssen Pharmaceuticals)	3–12 mg
Quetiapine	300–450 mg
Risperidone	4–6 mg

a Doses specific to short-term management of severe anxiety not reported.

orally or as a depot injection (i.e. antipsychotic injected in a formulation that releases the drug slowly over a period of time, with injections typically repeated every 2–4 weeks).

When used as an adjunctive treatment for treatment-resistant anxiety or depression, antipsychotics have predominantly been added to a SSRI (typically fluoxetine).[63,78] A systematic review of augmentation of pharmacotherapy in treatment-resistant anxiety disorders found that augmentation of ongoing therapy with an antipsychotic significantly reduced symptoms of anxiety in OCD (seven RCTs involving 198 people; SMD of −0.68, 95% CI −1.13 to −0.24).[63]

Common adverse effects associated with first-generation antipsychotics include extrapyramidal symptoms (which involve motor control).[76] Compared with second-generation antipsychotics, first-generation antipsychotics increase the risk of hyperprolactinaemia. By contrast, adverse effects occurring more frequently with second-generation antipsychotics are weight gain and metabolic abnormalities.[76] Among the second-generation antipsychotics, paliperidone (Invenga®, Janssen Pharmaceuticals) may cause restlessness and rapid heartbeat, whereas quetiapine is most commonly associated with constipation and dry mouth. Ziprasidone (Geodon®, Pfizer) and aripiprazole (Abilify®, Otsuka and Bristol-Myers Squibb) are more likely to be associated with headache, nausea and constipation, but only minor weight gain.

Antipsychotic drugs should be used with caution in people with cardiovascular disease, epilepsy (and conditions predisposing to seizures), depression, myasthenia gravis, prostatic hypertrophy or a susceptibility to angle-closure glaucoma.[60] Caution is also recommended in severe respiratory disease and in patients with a history of jaundice or who have blood dyscrasias (perform blood counts if unexplained infection or fever develops).

When prescribing antipsychotics to older adults, the balance of risks and benefits should be considered.[60] Antipsychotic drugs have been found to be associated with a small increased risk of mortality and an increased risk of stroke or transient ischaemic attack in older adults with dementia. When prescribed, it is recommended that initial doses of antipsychotic drugs for older adults be reduced to half the recommended adult dose or less (adult doses as listed in the BNF presented in *Table 6*), and that dosage could be adjusted further after accounting for individual factors such as weight, comorbidity and concomitant medication.[60]

Other drugs used as an anxiolytic

Other drug treatments used to treat the symptoms of anxiety include propranolol (beta-blocker). pregabalin (anticonvulsant) and buspirone (anxiolytic).

Propranolol is a non-selective beta-blocker, acting by inhibiting the binding of adrenaline and other stress hormones to the beta adrenoreceptor. Propranolol is primarily used to treat tremor, angina, high blood pressure, heart rhythm disorders and other heart or circulatory conditions.[60] In anxiety disorders propranolol might be used (typical dose of 40 mg once daily) when symptoms such as palpitation, sweating and tremor are present.[60] Common adverse effects associated with propranolol are gastrointestinal disturbances, low energy, trouble sleeping and feeling weak.

Pregabalin is a structural analogue of GABA but, unlike benzodiazepines, it does not bind directly to GABA receptors.[79] It is thought to elicit an anxiolytic effect through binding to a subunit of voltage-gated calcium channels in 'overexcited' presynaptic neurones in a state-dependent manner, thereby reducing the release of neurotransmitters, including glutamate and noradrenaline. Pregabalin is licensed for the treatment of GAD at a starting dose of 150 mg in two or three divided doses.[60] As with benzodiazepines, there are concerns about the tolerance of pregabalin during long-term treatment of anxiety disorders and the risk of symptoms of withdrawal on cessation of treatment.[79] Findings from preclinical studies and studies in healthy volunteers are disparate, and uncertainty remains whether or not the long-term use of pregabalin might be associated with similar issues observed during prolonged treatment with benzodiazepines.[79] Dizziness, drowsiness, dry mouth and constipation are recognised adverse effects when taking pregabalin.

Buspirone is a partial agonist of certain serotonin receptors (i.e. it binds to, and activates, a specific serotonin receptor, but has only partial efficacy compared with a full agonist).[80] Primarily used to treat GAD, the pharmacological profile of buspirone is different from other anxiolytics in that it alleviates symptoms of anxiety without the associated effects of sedation or functional impairment. In addition, the unique profile of buspirone means that use is not associated with dependence or with the risk of symptoms of withdrawal when treatment is discontinued. The usual dose of buspirone is 15–30 mg daily in divided doses, with a maximum dose of 45 mg daily. Common adverse effects of buspirone include dizziness, headache, drowsiness and nervousness.[60]

Chapter 2 Definition of the decision problem

Decision problem

The population of interest is older people (defined as aged ≥ 65 years) who have a primary diagnosis of an anxiety disorder without a known physical cause and whose symptoms of anxiety have not improved despite treatment with an intervention for which there is evidence of clinical effectiveness in the treatment of anxiety.

Pharmacological interventions used for the treatment of anxiety disorders were evaluated in the review and were not restricted to those licensed in Europe. Additionally, psychological and alternative therapies were also considered. Interventions were eligible when given as a monotherapy or in combination with another intervention for the treatment of anxiety. Interventions were compared with each other, both as a monotherapy and in combination with another intervention.

The primary outcome of interest is a reduction in symptoms of anxiety as determined by a validated disease-specific outcome measure: dichotomous and continuous measures of response to treatment were to be reported. A clinically meaningful improvement in response would be determined by the outcome measure used.

Secondary outcomes of interest are:

- response (defined as proportion of people experiencing ≥ 50% reduction in symptom score from baseline)
- remission (as defined in the individual studies)
- functional disability (encompasses effect on work, social interaction and family life)
- sleep quality
- development of, or change in, symptoms of depression
- adherence to treatment
- QoL
- carer outcomes (including carers' well-being, experience of care-giving and carers' needs for professional support)
- adverse effects (all-cause for any identified intervention).

Key issues

Treatment-resistant anxiety disorders have been the focus of numerous RCTs. Despite the burgeoning research in this field, as in treatment-resistant depression, criteria for treatment resistance and response and remission vary across studies, with some studies not reporting clear criteria. RCTs have defined resistance as inadequate response to treatment, but with no further detail on what would be classed as an inadequate response. As in treatment-resistant depression, treatment resistance in anxiety disorders has also been determined by no response after treatment with at least two antidepressants at adequate doses.[81–85] Again, studies vary in the required duration and adequate dosage of standard treatment. As noted earlier, categorisation of treatment resistance in anxiety disorders is further complicated by the nature of the disorders. Reduction in severity of symptoms does not necessarily denote response to treatment, and continued anxiety after treatment could suggest inadequate initial treatment or a natural transient reaction to a supervening stress factor rather than non-response. Variation in the criteria used across studies, and the complexity associated with evaluating anxiety disorders, contribute to the difficulty in interpreting the comparative clinical effectiveness of treatments from the limited evidence available.

It has been noted that populations enrolled across clinical trials evaluating treatments for older adults with anxiety disorders have not been, in the main, representative of older adults in general, in terms of age, functional status, ethnicity or medical health.[3] People enrolled in clinical trials are relatively homogeneous, having a specific disorder and few or no comorbidities, which does not perhaps represent older adults in general who typically have several comorbid physical or mental health illnesses.[86] Also, most trials have been carried out in an academic setting, with set treatment guides and set follow-up, which is atypical of the setting in which most older adults would receive care for their anxiety disorder.

Overall aims and objectives of assessment

The aim of the report was to evaluate the clinical effectiveness of medical, psychological and alternative therapies for treatment-resistant anxiety in older people. The lack of data assessing interventions in older people with treatment-resistant anxiety precluded achievement of the aim of the report. Potential areas for further research in the clinical area are outlined in *Chapter 3 (Assessment of clinical effectiveness)*.

Chapter 3 Assessment of clinical effectiveness

Methods for reviewing effectiveness

The aim of the systematic review was to evaluate the clinical effectiveness of any intervention (i.e. pharmacological, psychological or alternative) used to treat anxiety, in older adults with a focus on the treatment of anxiety that had not improved after treatment with an intervention for which there is evidence of clinical effectiveness in treating anxiety. Evidence was assessed by conducting a systematic review of the published research literature. The review was undertaken following the general principles published by the Centre for Reviews and Dissemination (CRD).[87] The protocol for the systematic review is registered on PROSPERO (registration number CRD42013005612).[88]

Identification of studies

Search strategies were designed to include medical subject headings (MeSH) and text terms for anxiety disorders (both as a collective term and as individual anxiety disorders), treatment failure and older adults. To maximise the number of potentially relevant studies retrieved, no MeSH or text terms were included for interventions of interest. Based on the results of the initial scoping search, it was anticipated that few RCTs that focused on older adults would be identified, despite the large number of studies retrieved. Therefore, the decision was taken to search additionally for prospective observational studies (matched control studies, case series and case–control studies). Search filters based on study design were identified via the InterTASC Information Specialists' Sub-Group search filter resource.[89] Filters developed and validated by the Scottish Intercollegiate Guidelines Network (SIGN) were used to identify RCTs in MEDLINE and EMBASE.[90] Filters devised by *Clinical Evidence* (a collection of systematic overviews covering various conditions) were chosen to retrieve potentially relevant observational studies from MEDLINE and EMBASE.[91] For the search of PsycINFO, filters implemented for study type were those designed by the University of Texas School of Public Health to retrieve RCTs and observational studies.[92] Search terms for anxiety, treatment resistance and older adults were tailored to the database searched. Bibliographies of previous reviews and retrieved articles were searched for additional studies. A clinical trial registry (ClinicalTrials.gov) was also searched to identify planned, on-going and finalised clinical trials of interest. In addition, clinical experts were contacted with a request for information on any additional studies of which they had knowledge. Conference abstracts that were reviewed and found not to report additional results to those presented in the relevant full publication were excluded.

The electronic databases searched were:

- MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE
- EMBASE
- The Cochrane Library [specifically Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews and Effects, and Health Technology Assessment Database]
- PsycINFO
- Web of Science.

Databases were searched from inception to September 2013 with the exception of Web of Science, and the initial search was carried out on 9 September 2013. Search parameters for Web of Science were limited to a search period of 2000–present, with study type restricted to article, meeting abstract, proceedings paper and corrections. Search results were uploaded into Reference Manager Version 11.0 (Thomson ResearchSoft, San Francisco, CA, USA) and deduplicated. Full details of the strategies are presented in *Appendix 3*.

Titles and abstracts returned by the search strategy were examined independently by two researchers [Charlotta Karner (CK) and Fatima Salih (FS)] and screened for possible inclusion. In cases where consensus could not be achieved, the full text of potentially relevant studies was ordered. During abstract appraisal, to facilitate discussion regarding whether or not sufficient evidence had been identified to restrict inclusion of study type to RCTs, potentially relevant studies were categorised as RCT, observational study or systematic review. To ensure that all relevant data were evaluated for inclusion, studies were not differentiated during appraisal of titles and abstracts based on age of the population, to allow for potential reporting of analysis of subgroups by age within the full text.

Full publications were assessed independently by two reviewers [Samantha Barton (SB) and CK] for inclusion or exclusion against prespecified criteria, with studies classified as a RCT evaluated first. After appraisal of full-text publications, the lack of RCTs meeting the prespecified inclusion criteria led to the evaluation of prospective observational studies for inclusion in the review. Disagreements on inclusion of a study, and on which consensus could not be reached, were resolved by discussion or input from a third reviewer [Steven J Edwards (SJE)].

Inclusion and exclusion criteria

Inclusion criteria were based on the decision problem outlined in *Chapter 2, Decision problem* (presented in *Table 7*). No restrictions were imposed on language of publication. Reference lists of identified systematic reviews were used as a source of potential additional studies, as well as a resource to compare studies retrieved from the systematic literature search. For the purposes of this review, a systematic review was defined as review reporting:

- a focused research question
- details of the search strategy, including databases searched and terms used, that would enable replication of the search
- inclusion/exclusion criteria, with clear definitions for population, intervention(s), comparator(s) and outcome(s) of interest
- critical appraisal of included studies.

Studies not meeting the prespecified inclusion criteria were excluded and studies specifying an age range as an inclusion criterion, and in which the upper age limit was 65 years, were excluded. Studies were also excluded if they were:

- trials reporting only post-crossover results and pre-crossover results could not be obtained
- case reports, historical articles, narrative reviews, editorials and opinion pieces
- reports published as only meeting abstracts and where insufficient methodological details were reported to allow critical appraisal of study quality.

Where it was not possible to determine the age of the included population (e.g. baseline characteristics not reported), authors were contacted with a request for additional information. No additional information was provided within the prespecified deadline for return of comments (1 month).

Planned data abstraction, critical appraisal, subgroup analyses and evidence synthesis procedures are documented in the review protocol.

Results of the review of clinical effectiveness evidence

No study, either RCT or observational, meeting the prespecified inclusion criteria was identified. The search of clinical trial registries identified no ongoing or planned RCTs in older adults with a treatment-resistant anxiety disorder. The emergence of systematic reviews evaluating the clinical effectiveness of

TABLE 7 Inclusion criteria

PICO	Criteria
Population	People aged ≥ 65 years with a primary diagnosis of an anxiety disorder and who are resistant/refractory to treatment
Anxiety and related disorders	Anxiety disorders specified as: • GAD • panic disorder (with or without agoraphobia) • social phobia (social anxiety disorder) • specific (simple phobia) • OCD • PTSD
Treatment resistance	Defined as no evidence of substantial improvement after 4 weeks' treatment with a treatment for which there is evidence of clinical effectiveness in the treatment of anxiety
Interventions	Any intervention (psychological, pharmacological or alternative) used to treat treatment-resistant anxiety. Interventions given alone or in combination (e.g. combination of psychological plus pharmacological interventions) would be included
Comparators	Any intervention versus placebo, no intervention (e.g. waiting list control) or another active intervention (including interventions given alone or in combination)
Outcomes	Primary outcomes: • reduction in symptoms of anxiety as determined by a validated disease-specific outcome measure (dichotomous and continuous measures of response to treatment will be included) Secondary outcomes: • response: defined as the proportion of people experiencing ≥ 50% reduction in symptom score from baseline • remission: defined as in the individual studies • functional disability (encompasses effect on work, social interaction and family life) • sleep quality • development of, or change in, symptoms of depression • adherence to treatment • QoL • carer outcomes (including carers' well-being, experience of care-giving and carers' needs for professional support) • adverse effects (all-cause for any identified intervention)
Study design	RCTs and comparative observational studies (prospective matched control studies, case series and case–control studies)
Other criteria	No restrictions on language or date of publication

PICO, population, intervention, comparator and outcome.

pharmacological and psychological treatments for anxiety in older adults highlights the increasing awareness of the need to manage this condition.[3,93,94]

Quantity and quality of research available

The searches retrieved a total of 3644 records (post deduplication) that were of possible relevance to the review (*Figure 1*). These were screened and 109 full references were ordered. Of the full references evaluated, the full publication of only one study was not obtained.[95] No study met the prespecified inclusion criteria outlined in *Table 7*.

The full list of studies screened and subsequently excluded (with reasons for exclusion) from the review is presented in *Appendix 4*.

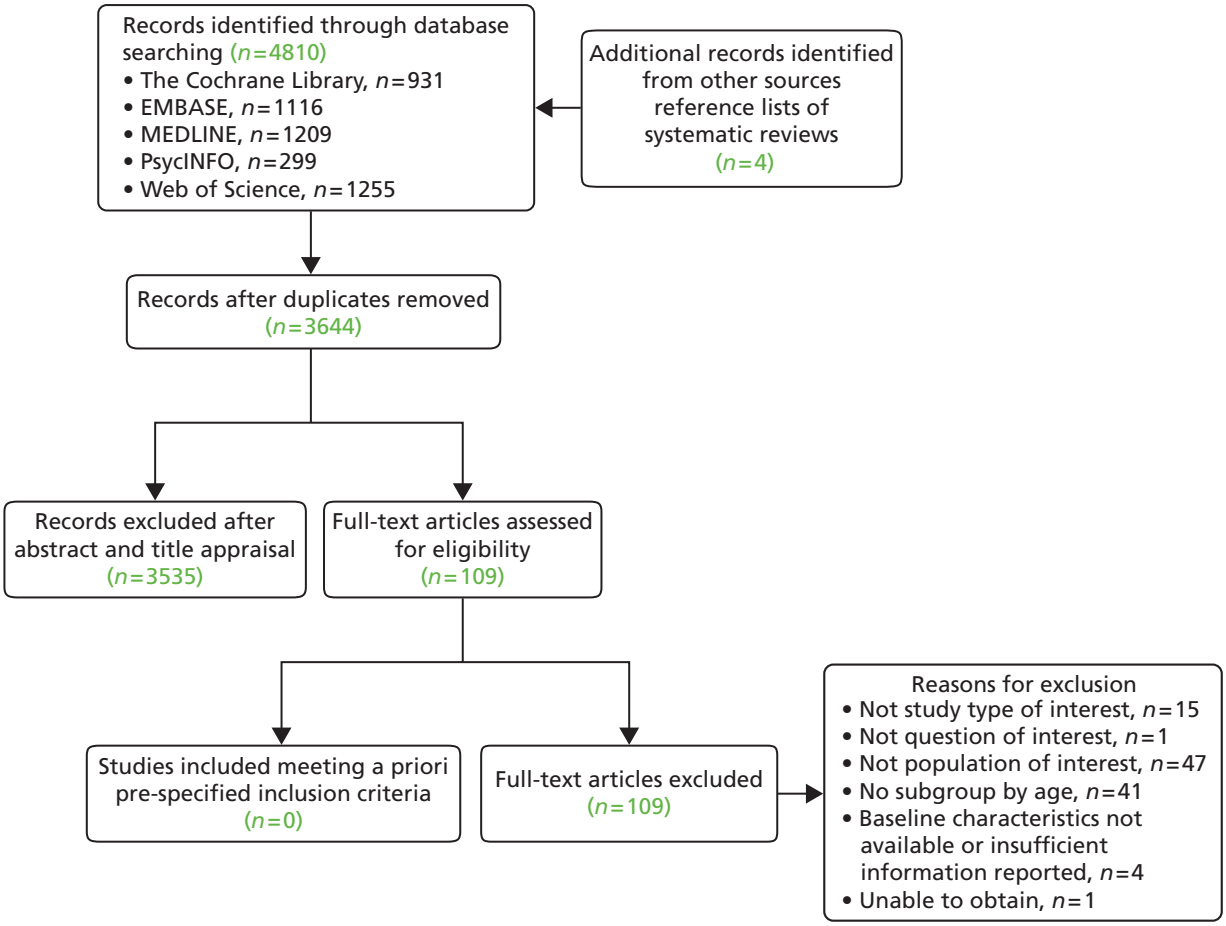

FIGURE 1 PRISMA flow diagram for studies included and excluded from the clinical effectiveness review.

Assessment of effectiveness

No study was identified that evaluated clinical effectiveness of interventions for treatment-resistant anxiety in older adults. Older adults present with manifestations of anxiety different from those of younger adults. Taken together with the finding that response to treatment is poorer in later life,[96] it might be that results from studies in younger adults with anxiety disorders cannot be applied to older adults. Considering treatment of anxiety disorders in older adults, systematic reviews of interventions for the treatment of anxiety in later life have found that psychological[93,97] and pharmacological[94] treatments are effective in reducing symptoms of anxiety in this population, with the authors of one review commenting that evidence is strongest for the treatment of GAD.[3] However, it has been noted that the studies identified by the reviews were small, with an average of 16 people and 43 people in these studies evaluating psychological and pharmacological treatments, respectively.[98] Although there is an increasing awareness of the difficulties in treating anxiety in older adults, there is a lack of an evidence base in this population.[98]

Chapter 4 Discussion

Statement of principal findings

This systematic review has highlighted the lack of an evidence base for the treatment of older adults with an anxiety disorder that have not responded, or has responded inadequately, to prior treatment. Although multiple RCTs were identified that evaluated clinical effectiveness of interventions for treatment-resistant anxiety disorders, many limited inclusion to adults aged 65 years and under. Of those studies that included people aged over 65 years, the mean ages reported at baseline suggest that most included people were younger than 65 years. The potentially small number of people likely to be aged 65 and over in the studies identified restricts the practicality and feasibility of carrying out a meta-analysis based on individual patient data. In addition, as the studies identified evaluated a range of treatments across various anxiety disorders, it is likely that the number of events for each treatment would be low, which would probably lead to considerable uncertainty in the results.

Strengths and limitations of the assessment

The review reported here is the first systematic review of interventions for treatment-resistant anxiety in older adults. The comprehensive methods implemented to carry out the review are a key strength of the research presented. However, the review highlights the lack of research in this area, identifying no comparative studies, which is a limitation.

Uncertainties

As no study was identified in older adults, there is considerable uncertainty as to which interventions might be clinically effective for older adults with an anxiety disorder that has not responded, or has responded inadequately, to prior treatment. Disparity between older and younger adults in the presentation of anxiety symptoms and in response to treatment could mean that results demonstrating the clinical effectiveness of interventions in treatment-resistant anxiety disorders in younger adults cannot necessarily be applied to older adults with comparable anxiety disorders.

Chapter 5 Conclusions

Implications for service provision

Identification and treatment of mental disorders is complex, and consideration of the needs and preferences of an individual is advocated when considering treatment choice. The review reported here supports conclusions from other studies that, at this time, the further management of treatment-resistant anxiety disorders in older adults cannot be guided by evidence from meta-analysis or RCTs. In older adults a common underlying reticence to discuss emotional symptoms, together with the misconception that anxiety is a natural part of the ageing process, means that older adults typically receive poorer mental health care than younger adults. The lack of high-level evidence in this area means that older adults are perhaps receiving inappropriate treatment or are not receiving a particular treatment because there is little evidence to support its use. At this time, there is scope to develop guidance on service provision and, as a consequence, to advance the standard of care received by older adults with an anxiety disorder in the primary and secondary settings.

Suggested research priorities

Studies evaluating interventions in older adults with an anxiety disorder that has not responded to first-line treatment are needed to address the lack of evidence in this clinical area. An important consideration would be the enrolment of older adults who would be representative of older adults in general, i.e. those with multiple comorbid physical and mental disorders that might require polypharmacy. In addition, it would be important to consider the setting in which the study was carried out to reflect the setting in which treatment is typically administered. In those taking multiple pharmacological agents, the properties of a particular drug could change considerably, leading to unexpected adverse effects as well as clinical effects. Therefore, assessment of adverse effects could be of equal importance to evaluation of clinical effectiveness.

Randomised controlled trials in anxiety disorders have often involved a heterogeneous population in terms of anxiety disorder, enrolling people with any form of anxiety disorder. As noted earlier, the different types of anxiety disorder respond to differing treatments and to varying degrees. Focusing on a particular anxiety disorder would be important to discern the most effective treatment for that disorder. However, acknowledged difficulties in defining and identifying treatment resistance in older adults could result in poor recruitment, both in terms of the low number of older adults likely to be categorised as treatment resistant and the heterogeneity in terms of prior treatment.

Anxiety disorders are typically chronic or episodic conditions, and maintaining an initial response is a key goal of treatment. Longitudinal studies that examine relapse or recurrence rates would provide an impression of the long-term effectiveness and acceptability of treatment interventions.

Given the often multiple drug treatment regimens taken by older adults, a focus on research into non-pharmacological treatments might be useful, building on currently implemented psychological therapies such as CBT. From the patient's perspective, developing uncomplicated, undemanding interventions that can be delivered at home or in groups might be warranted. Physical frailty, which is common in older adults, might preclude older adults from accessing services that are some distance from their home.

Difficulties encountered when undertaking RCTs in older adults include the perceptions of health professionals and practical problems relating to attending for regular assessments.[99] From the patient perspective, older adults have expressed fear of trial treatment and a dislike of the randomisation process.[1,3,99] Issues with transport, time taken to be involved in the trial and concerns about compromising current care are also barriers, generally, to patient participation in a clinical trial.[99] To overcome these potential barriers, a prospective matched control observational study might be an appropriate study design.

In summary, studies focusing on a specific anxiety disorder in older adults who have not responded, or have made an inadequate response, to prior treatment are warranted, with a suggested initial focus on effectiveness of non-pharmacological treatments. Given the epidemiological evidence that GAD is the most common anxiety disorder affecting older adults, initial studies evaluating treatments for this disorder might give greatest clinical benefit to a wider population base. Furthermore, the typically chronic nature of anxiety disorders is such that longitudinal studies to monitor maintenance of treatment effect would be needed to provide an insight into the long-term effectiveness and acceptability of treatments.

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Contributions of authors

Samantha Barton Provided overall project management, designed and carried out literature searches for the systematic review, assessed full publications for inclusion, wrote and contributed to the editing of the report.

Charlotta Karner Assessed abstracts and titles for inclusion, assessed full publications for inclusion and contributed to the editing of the report.

Fatima Salih Assessed abstracts and titles for inclusion, and contributed to the editing of the report.

David S Baldwin Provided clinical input into the design of the literature search, advised on clinical matters and contributed to the editing of the report.

Steven J Edwards Contributed to the editing of the report and was overall director of the project and guarantor of the report.

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Appendix 1 Diagnostic criteria for anxiety disorders set out in DSM-IV and ICD-10 classification systems

DSM-IV diagnostic criteria[9,100]	ICD-10 diagnostic criteria[11]
GAD	
A. Excessive anxiety and worry (apprehensive expectation), occurring on more days than not for at least 6 months, about a number of events or activities (such as work or school performance)	A. A period of at least six months with prominent tension, worry and feelings of apprehension, about every-day events and problems
B. The person finds it difficult to control the worry	B. At least four symptoms out of the following list of items must be present, of which at least one from items 1 to 4 *Autonomic arousal symptoms* 1. palpitations or pounding heart, or accelerated heart rate 2. sweating 3. trembling or shaking 4. dry mouth (not owing to medication or dehydration) *Symptoms concerning chest and abdomen* 5. difficulty breathing 6. feeling of choking 7. chest pain or discomfort 8. nausea or abdominal distress (e.g. churning in stomach) *Symptoms concerning brain and mind* 9. feeling dizzy, unsteady, faint or light-headed 10. feelings that objects are unreal (derealisation), or that one's self is distant or 'not really here' (depersonalisation) 11. fear of losing control, going crazy or passing out 12. fear of dying *General symptoms* 13. hot flushes or cold chills 14. numbness or tingling sensations *Symptoms of tension* 15. muscle tension, or aches and pains 16. restlessness and inability to relax 17. feeling keyed up, or on edge, or of mental tension 18. a sensation of a lump in the throat, or difficulty with swallowing *Other non-specific symptoms* 19. exaggerated response to minor surprises or being startled 20. difficulty in concentrating, or mind going blank, because of worrying or anxiety 21. persistent irritability 22. difficulty getting to sleep because of worrying

DSM-IV diagnostic criteria[9,100]	ICD-10 diagnostic criteria[11]
C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months). Note that only one item is required in children 1. Restlessness or feeling keyed up or on edge 2. Being easily fatigued 3. Difficulty concentrating or mind going blank 4. Irritability 5. Muscle tension 6. sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)	C. The disorder does not meet the criteria for panic disorder, phobic anxiety disorders, obsessive–compulsive disorder or hypochondriacal disorder
D. The focus of the anxiety and worry is not confined to features of an Axis I disorder, e.g. the anxiety or worry is not about having a panic attack (as in panic disorder), being embarrassed in public (as in social phobia), being contaminated (as in obsessive–compulsive disorder), being away from home or close relatives (as in separation anxiety disorder), gaining weight (as in anorexia nervosa), having multiple physical complaints (as in somatization disorder), or having a serious illness (as in hypochondriasis), and the anxiety and worry do not occur exclusively during PTSD	D. Most commonly used exclusion criteria: not sustained by a physical disorder, such as hyperthyroidism, an organic mental disorder or psychoactive substance-related disorder, such as excess consumption of amphetamine-like substances, or withdrawal from benzodiazepines
E. The anxiety, worry or physical symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning	
F. The disturbance is not caused by the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hyperthyroidism) and does not occur exclusively during a mood disorder, a psychotic disorder, or a pervasive developmental disorder	
Obsessive–compulsive disorder	
A. Either obsessions or compulsions: *Obsessions* as defined by (1), (2), (3) and (4): 1. recurrent and persistent thoughts, impulses or images that are experienced, at some time during the disturbance, as intrusive and inappropriate, and that cause marked anxiety or distress 2. the thoughts, impulses or images are not simply excessive worries about real-life problems 3. the person attempts to ignore or suppress such thoughts, impulses or images, or to neutralise them with some other thought or action 4. the person recognises that the obsessional thoughts, impulses or images are a product of his or her own mind (not imposed from without as in thought insertion) *Compulsions* as defined by (1) and (2): 1. Repetitive behaviours (e.g. hand washing, ordering, checking) or mental acts (e.g. praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly 2. The behaviours or mental acts are aimed at preventing or reducing distress, or preventing some dreaded event or situation. However, these behaviours or mental acts either are not connected in a realistic way with what they are designed to neutralise or prevent, or are clearly excessive	A. Either obsessions or compulsions (or both), present on most days for a period of at least 2 weeks

DSM-IV diagnostic criteria[9,100]	ICD-10 diagnostic criteria[11]
B. At some point during the course of the disorder the person has recognised that the obsessions or compulsions are excessive or unreasonable. Note that this does not apply to children	B. Obsessions (thoughts, ideas or images) and compulsions (acts) share the following features, all of which must be present: 1. they are acknowledged as originating in the mind of the patient and are not imposed by outside persons or influences 2. they are repetitive and unpleasant, and at least one obsession or compulsion must be present that is acknowledged as excessive or unreasonable 3. the subject tries to resist them (but if very long-standing, resistance to some obsessions or compulsions may be minimal). At least one obsession or compulsion must be present that is unsuccessfully resisted 4. carrying out the obsessive thought or compulsive act is not in itself pleasurable (this should be distinguished from the temporary relief of tension or anxiety)
C. The obsessions or compulsions cause marked distress, are time-consuming (take more than 1 hour a day, or significantly interfere with the person's normal routine, occupational (or academic) functioning or usual social activities or relationships	C. The obsessions or compulsions cause distress or interfere with the subject's social or individual functioning, usually by wasting time.
D. If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g. preoccupation with food in the presence of an eating disorder; hair pulling in the presence of trichotillomania; concern with appearance in the presence of body dysmorphic disorder; preoccupation with drugs in the presence of a substance use disorder; preoccupation with having a serious illness in the presence of hypochondriasis; preoccupation with sexual urges or fantasies in the presence of a paraphilia; or guilty ruminations in the presence of major depressive disorder)	D. Most commonly used exclusion criteria: not caused by other mental disorders, such as schizophrenia and related disorders, or mood (affective) disorders
E. The disturbance is not caused by the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition	
Panic disorder[a]	
A. Both (1) and (2): i. recurrent unexpected panic attacks ii. at least one of the attacks has been followed by 1 month (or more) of one (or more) of the following: iii. persistent concern about having additional attacks iv. worry about the implications of the attack or its consequences (e.g. losing control, having a heart attack, 'going crazy') v. a significant change in behaviour related to the attacks	A. Recurrent panic attacks that are not consistently associated with a specific situation or object and often occurring spontaneously (i.e. the episodes are unpredictable). The panic attacks are not associated with marked exertion or with exposure to dangerous or life-threatening situations
B. Absence of agoraphobia/presence of agoraphobia	B. A panic attack is characterised by all of the following: (a) it is a discrete episode of intense fear or discomfort (b) it starts abruptly (c) it reaches a crescendo within a few minutes and lasts at least some minutes (d) at least four symptoms must be present from the list below, one of which must be from items 1 to 4:

DSM-IV diagnostic criteria[9,100]	ICD-10 diagnostic criteria[11]
	Autonomic arousal symptoms 1. palpitations or pounding heart, or accelerated heart rate 2. sweating 3. trembling or shaking 4. dry mouth (not caused by medication or dehydration) *Symptoms concerning chest and abdomen* 5. difficulty breathing 6. feeling of choking 7. chest pain or discomfort 8. nausea or abdominal distress (e.g. churning in stomach) *Symptoms concerning brain and mind* 9. feeling dizzy, unsteady, faint or light-headed 10. feelings that objects are unreal (derealisation), or that one's self is distant or 'not really here' (depersonalisation) 11. fear of losing control, going crazy or passing out 12. fear of dying *General symptoms* 13. hot flushes or cold chills 14. numbness or tingling sensations
C. The panic attacks are not caused by the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hyperthyroidism)	C. Most commonly used exclusion criteria: not caused by a physical disorder, organic mental disorder, or other mental disorder such as schizophrenia and related disorders, affective disorders or somatoform disorders
D. The panic attacks are not better accounted for by another mental disorder, such as social phobia (e.g. occurring on exposure to feared social situations), specific phobia (e.g. exposure to a specific phobic situation), OCD (e.g. on exposure to dirt in someone with an obsession about contamination), PTSD (e.g. in response to stimuli associated with a severe stressor) or separation anxiety disorder (e.g. in response to being away from home or close relatives)	
PTSD	
A. The person has been exposed to a traumatic event in which both of the following were present: 1. the person experienced, witnessed, or was confronted with an event, or events, that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others 2. the person's response involved intense fear, helplessness or horror. Note that in children this may be expressed instead by disorganised or agitated behaviour	A. Exposure to a stressful event or situation (either short or long lasting) of exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress in almost anyone
B. The traumatic event is persistently re-experienced in one (or more) of the following ways: 1. recurrent and intrusive distressing recollections of the event, including images, thoughts or perceptions. Note that in young children repetitive play may occur in which themes or aspects of the trauma are expressed	B. Persistent remembering or 'reliving' the stressor by intrusive flash backs, vivid memories, recurring dreams or by experiencing distress when exposed to circumstances resembling or associated with the stressor

DSM-IV diagnostic criteria[9,100]	ICD-10 diagnostic criteria[11]
2. recurrent distressing dreams of the event. Note that in children these may be frightening dreams without recognisable content 3. acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations and dissociative flashback episodes, including those that occur on awakening or when intoxicated). Note that in young children trauma-specific re-enactment may occur 4. intense psychological distress at exposure to internal or external cues that symbolise or resemble an aspect of the traumatic event; physiological reactivity on exposure to internal or external cues that symbolise or resemble an aspect of the event	
C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following: 1. efforts to avoid thoughts, feelings or conversations associated with the trauma 2. efforts to avoid activities, places or people who arouse recollections of the trauma 3. inability to recall an important aspect of the trauma 4. markedly diminished interest or participation in significant activities 5. feeling of detachment or estrangement from others 6. restricted range of affect (e.g. unable to have loving feelings) 7. sense of a foreshortened future (e.g. does not expect to have a career, marriage, children or a normal life span)	C. Actual or preferred avoidance of circumstances resembling, or associated with, the stressor (not present before exposure to the stressor)
D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following: i. difficulty falling or staying asleep ii. irritability or outbursts of anger iii. difficulty concentrating iv. hypervigilance v. exaggerated startle response	D. Either (1) or (2): 1. inability to recall, either partially or completely, some important aspects of the period of exposure to the stressor 2. persistent symptoms of increased psychological sensitivity and arousal (not present before exposure to the stressor), shown by any two of the following: i. difficulty in falling or staying asleep ii. irritability or outbursts of anger iii. difficulty in concentrating iv. hypervigilance v. exaggerated startle response
E. Duration of the disturbance (symptoms in Criteria B, C and D) is more than 1 month F. The disturbance causes clinically significant distress or impairment in social, occupational or other important areas of functioning	E. Criteria B, C and D all occurred within six months of the stressful event or the end of a period of stress (for some purposes, onset delayed more than six months may be included but this should be clearly specified separately)

DSM-IV diagnostic criteria[9,100]	ICD-10 diagnostic criteria[11]
Social anxiety disorder	
A. A marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing. Note: in children, there must be evidence of the capacity for age-appropriate social relationships with familiar people and the anxiety must occur in peer settings, not just interactions with adults	A. Either (1) or (2): 1. marked fear of being the focus of attention or fear of behaving in a way that will be embarrassing or humiliating 2. marked avoidance of being the focus of attention or situations in which there is fear of behaving in an embarrassing or humiliating way These fears are manifested in social situations, such as eating or speaking in public; encountering known individuals in public; or entering or enduring small group situations, such as parties, meetings and classrooms
B. Exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed Panic attack. Note: in children, the anxiety may be expressed by crying, tantrums, freezing, or shrinking from social situations with unfamiliar people	B. At least two symptoms of anxiety in the feared situation at some time since the onset of the disorder, as defined in criterion B for agoraphobia and in addition one of the following symptoms: 1. blushing 2. fear of vomiting 3. urgency or fear of micturition or defaecation
C. The person recognises that the fear is excessive or unreasonable. Note: in children, this feature may be absent	C. Significant emotional distress caused by the symptoms or by the avoidance
D. The feared social or performance situations are avoided or else are endured with intense anxiety or distress	D. Recognition that the symptoms or the avoidance are excessive or unreasonable
E. The avoidance, anxious anticipation, or distress in the feared social or performance situation(s) interferes significantly with the person's normal routine, occupational (academic) functioning, or social activities or relationships, or there is marked distress about having the phobia	E. Symptoms are restricted to, or predominate in, the feared situation or when thinking about it
F. In individuals under age 18 years, the duration is at least 6 months	F. Most commonly used exclusion criteria: Criteria A and B are not caused by delusions, hallucinations or other symptoms of disorders such as organic mental disorders, schizophrenia and related disorders, affective disorders or OCD, and are not secondary to cultural beliefs
G. The fear or avoidance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition and is not better accounted for by another mental disorder (e.g., panic disorder with or without agoraphobia, separation anxiety, body dysmorphic disorder, a pervasive developmental disorder, or schizoid personality disorder)	
H. If a general medical condition or another mental disorder is present, the fear in Criterion A is unrelated to it, e.g. the fear is not of stuttering, trembling in Parkinson's disease, or exhibiting abnormal eating behaviour in anorexia nervosa	

a The DSM-IV distinguishes panic disorder with agoraphobia from panic disorder without agoraphobia; as indicated by criterion B under the heading of panic disorder.

Appendix 2 Doses of selective reuptake inhibitors for individual anxiety disorders as listed in the *British National Formulary*[60]

Drug	Brand name	Manufacturer	Dose
SSRIs			
Escitalopram	Cipralex®	H. Lundbeck A/S	*GAD and OCD* • 10 mg once daily, increased to a maximum of 20 mg daily, if required • older adults: initially half adult dose and a maximum of 10 mg daily *Panic disorder, with or without agoraphobia* • initial dose of 5 mg for the first week before increasing the dose to 10 mg daily. Dose can be further increased up to a maximum of 20 mg daily • older adults: initially half adult dose, and a maximum of 10 mg daily *Social anxiety disorder* • 10 mg once daily, adjusted after 2–4 weeks. Usual dose of 5–20 mg daily, dependent on response • older adults: not recommended
Sertraline (unlicensed)	Lustral®	Pfizer	*Panic disorder, with or without agoraphobia, social anxiety disorder and PTSD* • initially 25 mg daily, increased after 1 week to 50 mg daily; if response is partial and if drug tolerated, dose increased in steps of 50 mg at intervals of at least 1 week to a maximum of 200 mg daily *OCD* • adult and child over 12 years initially 50 mg daily, increased if necessary in steps of 50 mg at intervals of at least 1 week to a maximum dose of 200 mg daily
Paroxetine	Seroxat®	GlaxoSmithKline	*Social anxiety disorder, PTSD and GAD* • recommended dose 20 mg each morning to a maximum dose of 50 mg daily • older adult: as above, but to a maximum dose of 40 mg daily *OCD* • initially 20 mg each morning, increased gradually in steps of 10 mg to recommended dose of 40 mg daily. Maximum dose of 60 mg daily • older adult: as above, but to a maximum dose of 40 mg daily *Panic disorder* • initially 10 mg each morning, increased gradually in steps of 10 mg to recommended dose of 40 mg daily. Maximum dose of 60 mg daily • older adult: as above, but to a maximum dose of 40 mg daily

Drug	Brand name	Manufacturer	Dose
Citalopram	Cipramil®	Lundbeck	*Panic disorder* • 10 mg daily, increased gradually if necessary in steps of 10 mg daily, usual dose 20–30 mg daily. Maximum dose of 40 mg daily • older adult: as above, but to a maximum dose of 20 mg daily
Fluoxetine	Prozac®	Lilly	*OCD* • 20 mg daily, increased gradually if necessary to a maximum of 60 mg daily • older adults: as above, but maximum dose is typically 40 mg daily, but 60 mg can be used
Fluvoxamine	Faverin®	Abbott Healthcare	*OCD* • initially 50 mg in the evening, increased gradually if necessary after some weeks to maximum of 300 mg daily (over 150 mg in divided doses); usual maintenance dose 100–300 mg daily
SNRIs			
Venlafaxine	Efexor® XL	Pfizer	*GAD* • 75 mg once daily, increased if necessary at intervals of at least 2 weeks. Maximum dose of 225 mg once daily *Social anxiety disorder* • 75 mg once daily, increased if necessary at intervals of at least 2 weeks. Maximum dose of 225 mg once daily
Duloxetine	Cymbalta®	Eli Lilly	*GAD* • 30 mg daily, increased if necessary to 60 mg once daily. Maximum dose of 120 mg daily

Appendix 3 Literature search strategies

TABLE 8 OVID: MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present (initially searched 9 September 2013)

#	Term	Number of identified studies
1	exp Anxiety Disorders/	67,490
2	((anxi$ adj2 disorder) or (neuro$ adj2 worr$) or (neuro$ adj2 state$)).tw.	12,999
3	(obsess$ adj2 compuls$).tw.	11,554
4	ocd.ti,ab.	5785
5	(post adj2 trauma$).tw.	20,194
6	ptsd.ti,ab.	12,360
7	(social adj2 (phobi$ or anxi$)).tw.	6584
8	panic.ti,ab.	11,765
9	**or/1-8**	98,677
10	exp Treatment Failure/	27,346
11	(refract$ or resistan$ or nonrespon$ or non-respons$ or unrespon$ or fail$ or (incomplet$ adj respon$) or (no$ adj2 respon$)).tw.	1,672,308
12	(inadequat$ respon$ or (sub$ adj2 respon$) or (poor$ adj respon$)).tw.	44,440
13	**or/10-12**	1,713,541
14	(adult$ or mature or full-grown or full grown or old$ or senior or elder or aged or geriatr$ or middleage$ or middle-age or late$ life or pension$ or late$ onset$).ti,ab.	2,076,736
15	exp Adult/	5,571,109
16	exp Aged/ or exp Middle Aged/ or exp Retirement/	3,866,883
17	**or/14-16**	6,602,926
18	limit 17 to ("middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")	3,863,723
19	**9 and 13 and 18**	2295
20	exp cohort studies/	1,351,785
21	cohort$.tw.	276,045
22	controlled clinical trial.pt.	89,120
23	epidemiologic methods/	30,831
24	limit 23 to yr=1966-1989	11,289
25	exp case-control studies/	655,023
26	(case$ and control$).tw.	331,389
27	(case$ and series).tw.	120,725
28	**or/20-22,24-27**	1,960,600
29	**19 and 28**	821
30	Randomized Controlled Trials as Topic/	101,374
31	randomized controlled trial/	384,981

continued

TABLE 8 OVID: MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present (initially searched 9 September 2013) (*continued*)

#	Term	Number of identified studies
32	Random Allocation/	81,084
33	Double Blind Method/	130,411
34	Single Blind Method/	19,282
35	clinical trial/	501,321
36	clinical trial, phase i.pt	15,983
37	clinical trial, phase ii.pt	26,581
38	clinical trial, phase iii.pt	9981
39	clinical trial, phase iv.pt	963
40	controlled clinical trial.pt	89,120
41	randomized controlled trial.pt	384,981
42	multicenter study.pt	179,583
43	clinical trial.pt	501,321
44	exp Clinical Trials as topic/	293,751
45	(clinical adj trial$).tw	222,887
46	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw	133,162
47	PLACEBOS/	33,587
48	placebo$.tw	166,857
49	randomly allocated.tw	16,984
50	(allocated adj2 random$).tw	19,557
51	**or/30-50**	1,209,986
52	case report.tw	200,646
53	letter/	821,957
54	historical article/	298,696
55	**or/52-54**	1,309,918
56	**51 not 55**	1,179,947
57	**19 and 56**	599
58	**29 or 57**	1209

TABLE 9 OVID: EMBASE (searched from inception to 9 September 2013)

#	Term	Number of identified studies
1	exp Anxiety Disorders/	140,768
2	((anxi$ adj2 disorder) or (neuro$ adj2 worr$) or (neuro$ adj2 state$)).tw.	16,558
3	(obsess$ adj2 compuls$).tw.	15,206
4	ocd.ti,ab.	7611
5	(post adj2 trauma$).tw.	25,631
6	ptsd.ti,ab.	14,870
7	(social adj2 (phobi$ or anxi$)).tw.	8321
8	panic.ti,ab.	15,072
9	**or/1-8**	171,198
10	exp Treatment Failure/	79,790
11	(refract$ or resistan$ or nonrespon$ or non-respons$ or unrespon$ or fail$ or (incomplet$ adj respon$) or (no$ adj2 respon$)).tw.	1,980,617
12	(inadequat$ respon$ or (sub$ adj2 respon$) or (poor$ adj respon$)).tw.	53,340
13	**or/10-12**	2,047,630
14	(adult$ or mature or full-grown or full grown or old$ or senior or elder or aged or geriatr$ or middleage$ or middle-age or late$ life or pension$ or late$ onset$).ti,ab.	2,527,084
15	aged/	2,201,410
16	exp middle aged/	1,154,678
17	exp pensioner/	868
18	exp retirement/	10,352
19	**or/14-18**	4,748,715
20	limit 19 to (adult < 18 to 64 years > or aged <65+ years>)	3,181,884
21	**9 and 13 and 20**	2680
22	exp cohort analysis/	157,783
23	exp longitudinal study/	64,462
24	exp prospective study/	249,085
25	exp follow up/	743,046
26	cohort$.tw.	359,921
27	exp case control study/	89,362
28	(case$ and control$).tw.	418,496
29	exp case study/	21,169
30	(case$ and series).tw.	155,754
31	**or/22-30**	1,769,502
32	**21 and 31**	772
33	Clinical trial/	892,685
34	Randomized controlled trial/	358,000
35	Randomization/	63,374

continued

TABLE 9 OVID: EMBASE (searched from inception to 9 September 2013) (*continued*)

#	Term	Number of identified studies
36	Single blind procedure/	18,220
37	Double blind procedure/	119,966
38	Crossover procedure/	38,383
39	Placebo/	237,722
40	Randomi?ed controlled trial$.tw.	93,836
41	Rct.tw.	12,545
42	Random allocation.tw.	1335
43	Randomly allocated.tw.	19,845
44	Allocated randomly.tw.	1942
45	(allocated adj2 random).tw.	814
46	Single blind$.tw.	14,148
47	Double blind$.tw.	146,578
48	(treble or triple) adj (blind$).tw.	352
49	Placebo$.tw.	200,245
50	Prospective study/	249,085
51	**or/33-50**	1,392,985
52	Case study/	21,169
53	Case report.tw.	261,442
54	Abstract report/ or letter/	903,642
55	**or/52-54**	1,180,920
56	**51 not 55**	1,355,531
57	**21 and 56**	576
58	**32 or 57**	1116

TABLE 10 Cochrane Controlled Trials Register (searched from inception to 9 September 2013)

#	Term	Number of identified studies
1	MeSH descriptor: [Anxiety Disorders] explode all trees	4447
2	((anxi* near/2 disorder) or (neuro* near/2 worr*) or (neuro* near/2 state*)):ti,ab,kw	3915
3	(obsess* near/2 compuls*):ti,ab,kw	1276
4	ocd:ti,ab,kw	594
5	(post near/2 trauma*):ti,ab,kw	1451
6	ptsd:ti,ab,kw	930
7	(social near/2 (phobi$ or anxi*)):ti,ab,kw	609
8	panic:ti,ab,kw	1885
9	**#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8**	8882
10	MeSH descriptor: [Treatment Failure] explode all trees	2537
11	refract* or resistan* or nonrespon* or non-respons* or unrespon* or fail* or (incomplet* adj respon*) or (no* near/2 respon*):ti,ab,kw	92,549
12	(inadequat* near/1 respon* or (sub* near/2 respon*) or (poor* near/1 respon*)):ti,ab,kw	4157
13	**#10 or #11 or #12**	95,403
14	MeSH descriptor: [Adult] explode all trees	1133
15	(adult* or mature or full-grown or full grown or old* or senior or elder or aged or geriatr* or middleage* or middle-age or late* life or pension* or late* onset*):ti,ab,kw	432,233
16	**#14 or #15**	432,233
17	**#9 and #13 and #16**	931

TABLE 11 PsycINFO (searched from inception to 9 September 2013)

#	Term	Number of identified studies
1	exp Anxiety Disorders/	58,238
2	((anxi$ adj2 disorder) or (neuro$ adj2 worr$) or (neuro$ adj2 state$)).tw.	12,854
3	(obsess$ adj2 compuls$).tw.	15,008
4	ocd.ti,ab.	6642
5	(post adj2 trauma$).tw.	8805
6	ptsd.ti,ab.	18,406
7	(social adj2 (phobi$ or anxi$)).tw.	10,397
8	panic.ti,ab.	13,143
9	**or/1-8**	81,499
10	(refract$ or resistan$ or nonrespon$ or non-respons$ or unrespon$ or fail$ or (incomplet$ adj respon$) or (no$ adj2 respon$)).tw.	192,150
11	(inadequat$ respon$ or (sub$ adj2 respon$) or (poor$ adj respon$)).tw.	10,291
12	**10 or 11**	200,653
13	(adult$ or mature or full-grown or full grown or old$ or senior or elder or aged or geriatr$ or middleage$ or middle-age or late$ life or pension$ or late$ onset$).ti,ab.	678,919
14	**9 and 12 and 13**	1516
15	((case* adj5 control*) or (case adj3 comparison*) or case-comparison or control group*).ti, ab. not "Literature Review".md.	62,969
16	(cohort or longitudinal or prospective or retrospective).ti,ab,id. or longitudinal study.md. or prospective study.md. or retrospective study.md. not "Literature Review".md.	169,825
17	**15 or 16**	226,508
18	**14 and 17**	145
19	clinical trials/ or "treatment outcome clinical trial".md. or ((randomi?ed adj7 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*)) or (controlled adj3 trial*) or (clinical adj2 trial*)).ti,ab,id.	68,682
20	**14 and 19**	179
21	**18 or 20**	299

TABLE 12 Web of Science (searched from 2000 to 9 September 2013)

#	Term	Number of identified studies
1	(anxiety disorder or neurotic or neurotic state or ocd or ptsd or post trauma or panic or phobia)	73,338
2	((inadequate response or poor response or refract* or resistan* or nonrespon* or non-respon* or unrespon* or fail))	1,067,419
3	(adult or old or senior or elder or aged or geriatr* or middleage* or middle-age* or late* life or pension* or late* onset)	2,053,501
4	#1 and #2 and #3	1422
5	Limit 4 to article, meeting abstract, proceeding paper or correction	1255

Appendix 4 Table of excluded studies with rationale

Excluded study	Reason for exclusion
Abelson *et al.*[101]	Not population of interest (all people aged < 65 years)
Aboujaoude *et al.*[102]	Not study type of interest (single arm)
Allgulander[103]	Not study type of interest (review)
Altamura *et al.*[104]	No subgroup by age
Amiaz *et al.*[105]	Not population of interest (inclusion criterion of age of 18–65 years)
Anderson *et al.*[106]	Not study type of interest (letter)
Atmaca *et al.*[107]	Not population of interest (all people aged < 65 years)
Barr *et al.*[108]	No subgroup by age
Bartzokis *et al.*[109]	Not population of interest (all people aged < 65 years)
Blank *et al.*[110]	Not population of interest (not treatment resistant)
Blay *et al.*[111]	Not study type of interest (review)
Brawman-Mintzer *et al.*[112]	No subgroup by age
Bresolin *et al.*[113]	Not population of interest (not treatment resistant)
Bruno[114]	No subgroup by age
Buchsbaum *et al.*[115]	No subgroup by age
Campanini *et al.*[116]	No subgroup by age
Carey *et al.*[117]	Not population of interest (all people aged < 65 years)
Carr *et al.*[118]	Not population of interest (all people aged < 65 years)
Crocq *et al.*[119]	Not population of interest (all people aged < 65 years)
Csigo *et al.*[120]	No subgroup by age
Dannon *et al.*[121]	No subgroup by age
David *et al.*[122]	No subgroup by age
Denys *et al.*[123]	Not population of interest (inclusion criterion of age of 18–65 years)
Depping *et al.*[124]	Not study type of interest (review)
Di *et al.*[125]	Not population of interest (all people aged < 65 years; inclusion criterion of age of 18–45 years)
Dick *et al.*[126]	No subgroup by age
Diniz *et al.*[127]	Not population of interest (inclusion criterion of age of 18–65 years)
Diniz *et al.*[128]	Not population of interest (inclusion criterion of age of 18–65 years)
Erzegovesi *et al.*[129]	Not population of interest (inclusion criterion of age of 18–65 years)
Fallon *et al.*[130]	Not population of interest (all people aged < 65 years)
Fava *et al.*[131]	No subgroup by age
Fineberg *et al.*[132]	No subgroup by age
Fineberg *et al.*[133]	Not study type of interest (review)
Geus *et al.*[134]	Not population of interest (inclusion criterion of age of 18–65 years)

Excluded study	Reason for exclusion
Ginsberg[95]	Unable to obtain
Goodman *et al.*[135]	Not population of interest (all people aged < 65 years)
Haghighi *et al.*[136]	No subgroup by age
Hinton *et al.*[137]	Baseline characteristics not reported
Hinton *et al.*[138]	No subgroup by age
Hinton *et al.*[139]	No subgroup by age
Hinton *et al.*[140]	No subgroup by age
Hirschmann *et al.*[141]	No subgroup by age
Hoffart *et al.*[142]	No subgroup by age
Hofmann *et al.*[143]	Not study type of interest (review)
Hollander *et al.*[144]	No subgroup by age
Huff *et al.*[145]	Not population of interest (inclusion criterion of age of 21–65 years)
Ipser *et al.*[63]	Not study type of interest (review)
Kampman[146]	Not population of interest (all people aged < 65 years)
Kang *et al.*[147]	No subgroup by age
Katz[148]	Not study type of interest (review)
Khan *et al.*[149]	Abstract only; insufficient information to assess
Kolivakis *et al.*[150]	Not study type of interest (book chapter)
Koran *et al.*[81]	Not population of interest (all people aged < 65 years)
Koran *et al.*[151]	Not population of interest (all people aged < 65 years; inclusion criterion of age of 18–55 years)
Koran *et al.*[152]	Not population of interest (all people aged < 65 years)
Kordon *et al.*[153]	Not population of interest (all people aged < 65 years)
Krystal *et al.*[82]	No subgroup by age
Li *et al.*[154]	Not population of interest (all people aged < 65 years)
Lippitz *et al.*[155]	Not population of interest (not treatment resistant)
Lohoff *et al.*[156]	Baseline characteristics not reported
Macklin *et al.*[157]	No subgroup by age
Maina *et al.*[158]	No subgroup by age
Mallet *et al.*[159]	Not population of interest (all people aged < 65 years)
Mansur *et al.*[160]	Not population of interest (inclusion criterion of age of 18–65 years)
Mantovani *et al.*[161]	No subgroup by age
Marshall *et al.*[162]	Not population of interest (not treatment resistant)
Matsunaga *et al.*[163]	No subgroup by age
Mavissakalian[164]	Not population of interest (includes people who are not treatment resistant)
McDougle *et al.*[165]	Not population of interest (all people aged < 65 years)
McDougle *et al.*[166]	No subgroup by age
McDougle *et al.*[167]	Not population of interest (most people aged < 65 years; only 2 people were aged ≥ 65 years)
McDougle *et al.*[168]	Not population of interest (all people aged < 65 years)
Menza *et al.*[169]	Not population of interest (inclusion criterion of age of 18–65 years)

Excluded study	Reason for exclusion
Mithoefer *et al.*[170]	No subgroup by age
Muscatello *et al.*[171]	No subgroup by age
Nakatani *et al.*[172]	Not study type of interest (single arm study; no control group)
Ninan *et al.*[173]	No subgroup by age
Nuttin *et al.*[174]	Not population of interest (all people aged < 65 years)
Okun *et al.*[175]	Not question of interest
Osuch *et al.*[176]	Not population of interest (all people aged < 65 years)
Oude Voshaar *et al.*[177]	Not study type of interest (review protocol)
Peet *et al.*[178]	No subgroup by age
Pittenger[179]	Not study type of interest (single arm study; no control group)
Pollack[180]	Not study type of interest (single arm study; no control group)
Pollack *et al.*[181]	No subgroup by age
Prasko *et al.*[182]	Not population of interest (all people aged < 65 years; inclusion criterion of age of 18–45 years)
Prasko *et al.*[183]	Not population of interest (all people aged < 65 years)
Raskind *et al.*[184]	Not population of interest (not treatment resistant)
Ravizza *et al.*[185]	No subgroup by age
Rickels *et al.*[186]	No subgroup by age
Sachdev *et al.*[187]	No subgroup by age
Sachdev *et al.*[83]	No subgroup by age
Sayyah *et al.*[188]	Not population of interest (all people aged < 65 years)
Schutters *et al.*[189]	Not population of interest (includes people who are not treatment-resistant)
Selvi *et al.*[190]	Not population of interest (inclusion criterion of age of 18–65 years)
Shapira *et al.*[191]	No subgroup by age
Simon *et al.*[192]	No subgroup by age
Simon *et al.*[193]	No subgroup by age
Simon *et al.*[194]	Not population of interest (all people aged < 65 years)
Skapinakis *et al.*[195]	Not study type of interest (review)
Stanley *et al.*[196]	Not population of interest (not treatment resistant)
Stein *et al.*[197]	Baseline characteristics not provided
Stein *et al.*[198]	No subgroup by age
Storch[84]	No subgroup by age
Tarrier *et al.*[199]	Not population of interest (not treatment resistant)
Thorén *et al.*[200]	Not population of interest (all people aged < 65 years)
van Balkom *et al.*[201]	No subgroup by age
Wurthmann *et al.*[202]	Not population of interest (inclusion criterion of age of 18–65 years)
Zhang *et al.*[85]	Not population of interest (all people aged < 65 years)

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