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

HTA REPORT



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

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# Abstract (488 words)

## ****Background****

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). The disorders share 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 has 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.

## ****Objectives****

To evaluate the effectiveness of pharmacological, psychological and alternative therapies in older adults with an anxiety disorder that has not responded, or has 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 in 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.

## ****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 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 that has not responded to prior treatment. The comprehensive methods implemented to carry out the review are a key strength of the research presented. However, the 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 that has 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.

## ****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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# ABBREVIATIONS

|  |  |
| --- | --- |
| Abbreviation | Description |
| BNF | British National Formulary |
| CBT | Cognitive behavioural therapy |
| 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 Disease |
| MeSH | Medical Subject Headings |
| mg | Milligram |
| NICE | National Institute for Health and Care Excellence |
| OCD | Obsessive-compulsive disorder |
| OR | Odds ratio |
| PTSD | Post-traumatic stress disorder |
| QoL | Quality of life |
| RCT | Randomised controlled trial |
| SNRI | Selective norepinephrine reuptake inhibitor |
| SMD | Standardised mean difference |
| SSRI | Selective serotonin reuptake inhibitor |
| TCA | Tricyclic antidepressant |
| UK | United Kingdom |
| WHO | World Health Organization |

# 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 has tended 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. 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. 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 of 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 in 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; quality of life; 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 and under. Of those studies that included people aged over 65 years, the mean ages reported at baseline suggest that most included people were of an age much 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 likely 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.

# 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). The 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, particularly in older people as there is the perception that older people are generally more worried than younger adults. Also, 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 a side effect to the treatment. 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 no resource that summarises the evidence for how effective the various treatments available are at treating resistant anxiety disorders in older people, or how the treatments 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 of treatment. No study assessing treatments for treatment-resistant anxiety in older adults was identified, underscoring the lack of research in this clinical area.

# 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 USA-based study (9,282 English-speaking respondents aged ≥18 years) reported the median age of 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 outcome of the anxiety disorder. Of other anxiety and psychological disorders, depression is the most common comorbidity among younger and older adults.(1) Of older people with a diagnosis of an anxiety disorder, studies suggest that between 13%(4) and 23%(5) of people aged 55 years and older will also meet criteria for diagnosis of major depressive disorder. One study in adults aged >70 years found that 29.4% of older people with an anxiety disorder had a comorbid depressive disorder.(6) By comparison, 20% of younger adults (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. 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-refractory 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 disorder are the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the World Health Organization’s International Classification of Diseases (ICD). 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 due to known physical cause (e.g., medical conditions and symptoms caused by drug misuse);
* anxiety disorder not otherwise specified (covers symptoms not meeting 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.(11) 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 ICD10 lists anxiety disorders under the general heading “Neurotic, stress-related and somatoform disorders”, which comprises the subgroups of:(12)

* 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, a 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 been recognised that older adults from ethnic minority groups often have different manifestations of anxiety, both of which 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 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, Generalized Anxiety Disorder 7 (GAD-7), 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 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 severity.(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 will be required to categorise the disorder (based on criteria in the DSM-V or ICD10).

Psychological and physical symptoms of anxiety are common across all anxiety disorders.(19) Difficulty concentrating, feelings of trepidation, stress and restlessness are typical psychological manifestations of anxiety, whereas fatigue, heart palpitations, and trembling are common physical symptoms experienced by people with anxiety. 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 ICD10 criteria for the individual anxiety disorders are presented in Appendix 1.

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 |
| Abbreviations used in table: GAD, generalised anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder. | |

### 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 risk in older adults (summarised in Table 2).(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)

Table 2. 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., on-going 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 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 |

When a threat is perceived, various brain 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), which is produced by the adrenal glands. Adrenaline triggers a physical response to stress, including increased heart rate, and increased breathing rate.(22) At the same time, another hormonal system, the hypothalamo-pituitary-adrenal axis, initiates a pathway involving several hormones and other messengers that culminates in the release of adrenal hormones called glucocorticoids, the most important of which is cortisol.(22;23) Cortisol causes a rapid release of body energy stores to maintain blood sugar levels and also suppresses 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 aging 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 norepinephrine, 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 in 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 formation of memories.(21) The hippocampus is involved in consolidating a life-threatening or traumatic event into a memory. Some studies suggest that the hippocampus is smaller in some people who have PTSD.(28-31) The observed decrease in size of the hippocampus was 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 (fraternal) 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 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. Predictors of response to treatment, or conversely non-response to treatment, in anxiety disorders have been investigated in various studies.(38) Factors thought to contribute to poor response to treatment have been divided into four categories (outlined in Table 3): 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.

Table 3. 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 is overlapping 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 |
| Lifecycles |

|  |
| --- |
| Patient related |
| Severity |
| Medical comorbidity |
| Psychiatric comorbidity |
| Noncompliance |
| 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 |

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 of onset of 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) 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% to 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, in 2007, 2.28 million were estimated to have an anxiety disorder, with 13% of those aged 65 or over.(45) Prevalence of anxiety disorders is even higher in older 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% to 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, and OCD) reported GAD to be the most common anxiety disorder affecting people in the UK, with a prevalence of 4.4%. 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 4).(1) Results reported in the review suggest that social phobia (with or without agoraphobia) and GAD have the largest estimates of prevalence. However, elsewhere, it has been reported that GAD is the most common anxiety disorder affecting older adults, with a prevalence of 3.1% to 11.2%.(3) The authors of the comprehensive review note that, because of methodological issues identified earlier, it is not possible to draw definitive conclusions on prevalence. Data on prevalence of treatment-resistant anxiety in older people were not identified.

Table 4. Estimated prevalence of anxiety disorders in older people(1)

|  |  |
| --- | --- |
| Anxiety disorder | Prevalence in older people |
| GAD | 1.2% to 7.3% |
| OCD | 0.1% to 0.8% |
| Social phobia | 3.1% to 10.2% |
| Specific phobia | Not reported |
| PTSD | 0.4% to 1.0% |
| Panic disorder | 0.1% to 1.0% |
| Abbreviations used in table: GAD, generalised anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder. | |

### Impact of health problem

Compared 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, fall, physical and functional disability, and loneliness.(1;3) Furthermore, presence of an anxiety disorder is associated with reduced compliance to medical treatment, and chronic conditions are potentially exacerbated, which can result in loss of independence and increased reliance on family or carers. Anxiety has a considerable detrimental effect on quality of life of both the older person with an anxiety disorder and that of 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 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 and 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 the patient with information to understand their disorder and the treatment options available is proposed as an important component 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% CI –1.03 to –0.69 [20 studies, N = 1,121]).(57) It should be noted that the evidence is based on a synthesis of data from trials in various anxiety disorders and moderate statistical heterogeneity (44%) was present. 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; low-intensity psychological interventions listed in CG113 are summarised in Table 5.(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 healthcare 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)

Table 5. Low-intensity interventions for generalised anxiety disorder described in NICE clinical guideline 113(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 healthcare 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 |
| Abbreviation used in table: CBT, cognitive behavioural therapy. | |

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 healthcare professionals; examples of high-intensity psychological interventions include cognitive behavioural therapy (CBT) and applied relaxation (additional examples are presented in Table 6). 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 an 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 the 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 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 an SSRI; benzodiazepines are most frequently used to manage insomnia, particularly in older adults when 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 fall 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 number of drugs administered.(62) Additionally, it is well recognised that adherence with 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, and lead to increased reliance on carers, and, ultimately, 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 and colleagues identified 28 randomised controlled trials (RCTs) evaluating addition of predominantly an antipsychotic (17 RCTs) to on-going pharmacotherapy.(63) Most RCTs evaluated short-term (average follow-up of 7 weeks) augmentation of an 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, and the way in which the body metabolises a drug or drugs 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 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 versus 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. Comprising multiple components that are typically adapted to an individual, high-intensity psychological techniques are complex and considerably more resource intensive than low-intensity psychological interventions; an overview of components of some high-intensity psychological therapies is presented in Table 6.

CBT (Table 6) 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. 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 (Table 6) is an alternative to CBT that has benefit in the treatment GAD(64) and panic disorder,(65) and trauma-focused CBT and eye movement desensitisation and reprocessing (Table 6) are used in the treatment of anxiety associated with PTSD.(49;66) 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 healthcare 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.

Table 6. High-intensity interventions for anxiety disorders(48;49)

|  |  |
| --- | --- |
| Intervention | Description |
| ***High intensity psychological treatments*** | |
| Cognitive behavioural therapy | 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, and 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. |

### Pharmacological treatments

For OCD, social anxiety disorder, GAD, and panic disorder, NICE guidance recommends offering an SSRI, and 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), 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, 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 be troublesome. Age-related changes in physiology could lead to increased volume of distribution of the drug or decreased drug clearance, both of which could lead to increased plasma drug concentrations and resulting adverse effects.(62)

Selective reuptake inhibitors

SSRIs 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 response to stress. Dysfunction of the biological pathways 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 level, 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 listed in the British National Formulary (BNF) are presented in Table 7. Oral doses for the individual SSRIs and SNRIs reported in the BNF are presented in Appendix 2.

Table 7. Selective reuptake inhibitors used for the treatment of anxiety disorders as specified in the British National Formulary(60)

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

SSRIs are the first choice of pharmacological treatment for anxiety disorders and major depression because they have better tolerability and adverse effect profile compared with other classes of antidepressants.(72) In particular, compared with tricyclic antidepressants (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 (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, or acute angle-closure glaucoma and 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 GABAA 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 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 (about 162,000 registered patients annually aged ≥65 years) found that, in 2003, benzodiazepines (52.4/1,000 people) was 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, norepinephrine, and dopamine.(72) Amitriptyline, clomipramine and dosulepin are examples of TCAs.(60) Some TCAs inhibit reuptake of serotonin to a greater extent, whereas others may predominantly block reuptake of norepinephrine. However, most TCAs inhibit reuptake of both serotonin and norepinephrine. 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, the 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 a dose of initially 25 mg daily, with an initial dose of 10 mg daily in older adults.(60) The dose can be increased over 2 weeks to 100–150 mg daily, and 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 fall and of fracture with use of TCAs.(75) Initially, a low dose should be used, and people should be monitored closely, particularly for psychiatric and cardiac adverse effects.(60)

TCA and related antidepressants should be used with caution in people with cardiovascular disease, epilepsy and 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 receptors means that caution is also needed when treating people with prostatic hypertrophy, chronic constipation, increased intra-ocular pressure, 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 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, 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 class listed in the BNF are summarised in Table 8.(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 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 an 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 (7 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](http://en.wikipedia.org/wiki/Extrapyramidal_symptoms) (which involve motor control).(76) Compared with second generation antipsychotics, first generation antipsychotics increase the risk of [hyperprolactinaemia](http://en.wikipedia.org/wiki/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 may cause restlessness, and rapid heartbeat, whereas quetiapine is most commonly associated with constipation and dry mouth. Ziprasidone and aripiprazole are more likely to be associated with headache, nausea, and constipation, but only a minor gain in weight.

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 8), and that dosage could be adjusted further after accounting for individual factors such as weight, comorbidity, and concomitant medication.(60)

Table . 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 (mg) |
| ***First-generation antipsychotics*** | |
| Chlorpromazine | 75–300 |
| Haloperidol | 500 micrograms twice daily |
| Pericyazine | 15–30 divided into 2 doses |
| Perphenazine | 12 |
| Prochlorperazine | 15–20 in divided doses |
| Trifluoperazine | 2–4 in divided doses |

|  |  |
| --- | --- |
|  | Usual daily dose (mg)a |
| ***Second-generation antipsychotics*** | |
| Amisulpride | 50–800 |
| Aripiprazole | 10–30 |
| Clozapine | 200–450 |
| Olanzapine | 10–20 |
| Paliperidone | 3–12 |
| Quetiapine | 300–450 |
| Risperidone | 4–6 |
| a Doses specific to short-term management of severe anxiety not reported.  Abbreviation used in table: mg, milligram. | |

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 epinephrine and other stress hormones to the beta receptor. 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 in a state-dependent manner to a subunit of voltage-gated calcium channels in ‘over-excited’ pre-synaptic neurones, thereby reducing the release of neurotransmitters, including glutamate, and norepinephrine. Pregabalin is licensed for the treatment of GAD at a starting dose of 150 mg in 2–3 divided doses.(60) Analogous to 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 as to whether 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. 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)

# 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 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;
* quality of life;
* 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 dose.(81-85) Again, studies vary in the required duration and adequate dose 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 *Section 3 (Assessment of clinical effectiveness)*.

# ASSESSMENT OF CLINICAL EFFECTIVENESS

## Methods for reviewing effectiveness

The aim of the systematic review was to evaluate the clinical effectiveness in older adults of any intervention (i.e., pharmacological, psychological, or alternative) used to treat anxiety, 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 would be identified that focused on older adults, 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.

Electronic databases searched were:

* MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R);
* 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(R).

Databases were searched from inception, 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 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 as to whether 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 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 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 Section 2.1 (presented in Table 9). 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.

Table 9. 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 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. |
| Abbreviations used in table: GAD, generalised anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; QoL, quality of life; RCTs, randomised controlled trials. | |

Studies not meeting the prespecified inclusion criteria (Table 9) were excluded: 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 allotted period of time.

Planned data abstraction, critical appraisal, subgroup analyses and evidence synthesis procedures are documented in the review protocol (Appendix 4).

## Results of the review of clinical effectiveness evidence

No study, either RCT or observational, meeting the prespecified inclusion criteria (Table 9) 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 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 3,644 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 9.

The full list of studies screened and subsequently excluded (with reasons for exclusion) from the review is presented in Appendix 5.

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, the studies identified by the reviews were small, with an average of 16 people and 43 people in 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)

# 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 has 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 of an age 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 likely 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 to or has responded inadequately to prior treatment. Disparity between older and younger adults in 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.

# 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, that is, 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.

RCTs 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 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 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.Acknowledgements

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# APPENDICES

## Appendix 1. Diagnostic criteria for anxiety disorders set out in DSM-IV and ICD10 classification systems

|  |  |
| --- | --- |
| DSM-IV diagnostic criteria(9) (adaptedfrom AnxietyUK(100)) | ICD10 diagnostic criteria(12) |
| ***Generalised anxiety disorder*** | |
| **A.** Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).  **B.** The person finds it difficult to control the worry.  **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: 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).  **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 Posttraumatic Stress Disorder.  **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 due to 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. | **A.** A period of at least six months with prominent tension, worry and feelings of apprehension, about every-day events and problems.  **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 due 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" (depersonalization);  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.  **C.** The disorder does not meet the criteria for panic disorder, phobic anxiety disorders, obsessive-compulsive disorder or hypochondriacal disorder.  **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. |
| ***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 neutralize them with some other thought or action;  4. the person recognizes 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 neutralize or prevent or are clearly excessive.  **B.** At some point during the course of the disorder, the person has recognised that the obsessions or compulsions are excessive or unreasonable. Note: This does not apply to children.  **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.  **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).  **E.** The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition. | **A.** Either obsessions or compulsions (or both), present on most days for a period of at least two weeks.  **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 which 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 distress or interfere with the subject's social or individual functioning, usually by wasting time.  **D.** Most commonly used exclusion criteria: not due to other mental disorders, such as schizophrenia and related disorders, or mood (affective) disorders. |
| ***Panic disordera*** | |
| **A.** Both (1) and (2):  1. Recurrent unexpected Panic Attacks;  2. At least one of the attacks has been followed by 1 month (or more) of one (or more) of the following:  a. Persistent concern about having additional attacks;  b. Worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, “going crazy”);  c. A significant change in behaviour related to the attacks.  **B.** Absence of agoraphobia/presence of agoraphobia.  **C.** The panic attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism).  **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), Obsessive-Compulsive Disorder (e.g., on exposure to dirt in someone with an obsession about contamination), Post-Traumatic Stress Disorder (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). | **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.** A panic attack is characterized 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:  ***Autonomic arousal symptoms***  1. palpitations or pounding heart, or accelerated heart rate.  2. sweating;  3. trembling or shaking;  4. dry mouth (not due 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.  **C.** Most commonly used exclusion criteria: not due to a physical disorder, organic mental disorder, or other mental disorders such as schizophrenia and related disorders, affective disorders, or somatoform disorders. |
| ***Post-traumatic stress disorder*** | |
| **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: In children, this may be expressed instead by disorganised or agitated behaviour  **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: In young children, repetitive play may occur in which themes or aspects of the trauma are expressed;  2. recurrent distressing dreams of the event. Note: In children, there may be frightening dreams without recognizable 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: In young children, trauma-specific re-enactment may occur;  4. intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event; physiological reactivity on exposure to internal or external cues that symbolize 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 that 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).  **D.** Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:  1. difficulty falling or staying asleep;  2. irritability or outbursts of anger;  3. difficulty concentrating;  4. hypervigilance;  5. 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. | **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.** 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.  **C.** Actual or preferred avoidance of circumstances resembling or associated with the stressor (not present before exposure to the stressor).  **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:  a. difficulty in falling or staying asleep;  b. irritability or outbursts of anger;  c. difficulty in concentrating;  d. hypervigilance;  e. exaggerated startle response.  **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.) |
| ***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.  **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.  **C.** The person recognises that the fear is excessive or unreasonable. Note: In children, this feature may be absent.  **D.** The feared social or performance situations are avoided or else are endured with intense anxiety or distress.  **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.  **F.** In individuals under age 18 years, the duration is at least 6 months.  **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 fro by another mental disorder (e.g., Panic Disorder With or Without Agoraphobia, Separation Anxiety, Body Dysmorphic Disorder, a Pervasisive 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.** 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.** 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.** Significant emotional distress due to the symptoms or to the avoidance.  **D.** Recognition that the symptoms or the avoidance are excessive or unreasonable.  **E.** Symptoms are restricted to or predominate in the feared situation or when thinking about it.  **F.** Most commonly used exclusion criteria: Criteria A and B are not due to delusions, hallucinations, or other symptoms of disorders such as organic mental disorders, schizophrenia and related disorders, affective disorders, or obsessive-compulsive disorder, and are not secondary to cultural beliefs. |
| 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® | Lundbeck | **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 max. 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. 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 |
| 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® | Abott 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; dose may be increased 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 1. 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$).tw. | 11,554 |
| 4 | ocd.ti,ab. | 5,785 |
| 5 | (post adj2 trauma$).tw. | 20,194 |
| 6 | ptsd.ti,ab. | 12,360 |
| 7 | (social adj2 (phobi$ or anxi$)).tw. | 6,584 |
| 8 | panic.ti,ab. | 11,765 |
| 9 | **or/1-8** | 98,677 |
| 10 | exp Treatment Failure/ | 27,346 |
| 11 | (refract$ 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$).ti,ab. | 2,076,736 |
| 15 | exp Adult/ | 5,571,109 |
| 16 | exp Aged/ or exp Middle Aged/ or exp Retirement/ | 3,866,883 |
| 17 | **or/14-16** | 6,602,926 |
| 18 | limit 17 to ("middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") | 3,863,723 |
| 19 | **9 and 13 and 18** | 2,295 |
| 20 | exp cohort studies/ | 1,351,785 |
| 21 | cohort$.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 |
| 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 | 9,981 |
| 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** | 1,209 |

Table 2. 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$).tw. | 15,206 |
| 4 | ocd.ti,ab. | 7,611 |
| 5 | (post adj2 trauma$).tw. | 25,631 |
| 6 | ptsd.ti,ab. | 14,870 |
| 7 | (social adj2 (phobi$ or anxi$)).tw. | 8,321 |
| 8 | panic.ti,ab. | 15,072 |
| 9 | **or/1-8** | 171,198 |
| 10 | exp Treatment Failure/ | 79,790 |
| 11 | (refract$ 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$).ti,ab. | 2,527,084 |
| 15 | aged/ | 2,201,410 |
| 16 | exp middle aged/ | 1,154,678 |
| 17 | exp pensioner/ | 868 |
| 18 | exp retirement/ | 10,352 |
| 19 | **or/14-18** | 4,748,715 |
| 20 | limit 19 to (adult <18 to 64 years> or aged <65+ years>) | 3,181,884 |
| 21 | **9 and 13 and 20** | 2,680 |
| 22 | exp cohort analysis/ | 157,783 |
| 23 | exp longitudinal study/ | 64,462 |
| 24 | exp prospective study/ | 249,085 |
| 25 | exp follow up/ | 743,046 |
| 26 | cohort$.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 |
| 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$.tw. | 93,836 |
| 41 | Rct.tw. | 12,545 |
| 42 | Random allocation.tw. | 1,335 |
| 43 | Randomly allocated.tw. | 19,845 |
| 44 | Allocated randomly.tw. | 1,942 |
| 45 | (allocated adj2 random).tw. | 814 |
| 46 | Single blind$.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** | 1,116 |

Table 3. Cochrane Controlled Trials Register (searched from inception to 9 September 2013)

|  |  |  |
| --- | --- | --- |
| # | Term | Number of identified studies |
| 1 | MeSH descriptor: [Anxiety Disorders] explode all trees | 4,447 |
| 2 | ((anxi\* near/2 disorder) or (neuro\* near/2 worr\*) or (neuro\* near/2 state\*)):ti,ab,kw | 3,915 |
| 3 | (obsess\* near/2 compuls\*):ti,ab,kw | 1,276 |
| 4 | ocd:ti,ab,kw | 594 |
| 5 | (post near/2 trauma\*):ti,ab,kw | 1,451 |
| 6 | ptsd:ti,ab,kw | 930 |
| 7 | (social near/2 (phobi$ or anxi\*)):ti,ab,kw | 609 |
| 8 | panic:ti,ab,kw | 1,885 |
| 9 | **#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8** | 8,882 |
| 10 | MeSH descriptor: [Treatment Failure] explode all trees | 2,537 |
| 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 | 4,157 |
| 13 | **#10 or #11 or #12** | 95,403 |
| 14 | MeSH descriptor: [Adult] explode all trees | 1,133 |
| 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 4. 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$).tw. | 15,008 |
| 4 | ocd.ti,ab. | 6,642 |
| 5 | (post adj2 trauma$).tw. | 8,805 |
| 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** | 1,516 |
| 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 5. 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 | 1,422 |
| 5 | Limit 4 to article, meeting abstract, proceeding paper or correction | 1,255 |

## Appendix 4. Final protocol

**HTA no 13/39: DRAFT PROTOCOL**

1. **Project title**

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

1. **Name of TAR team and project ‘lead’**

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1. **Plain English Summary**

Anxiety disorders include generalised anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, and phobia (an intense fear of an object or situation). Although each anxiety disorder has its own set of symptoms, overwhelming feelings of fear and worry are common. Most people with an anxiety disorder are diagnosed by the age of 40, but a few people will develop an anxiety disorder when they get older (after the age of 65 years). Anxiety disorders can be difficult to recognise, particularly in older people as there is the perception that older people are generally more worried than younger adults. Also, older people tend to be more 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, drug treatments and complementary therapies. Psychological treatments are aimed at helping people develop an understanding of their condition and learn new skills to manage their mental health. In older people, not only is it more difficult to recognise an anxiety disorder, choosing a treatment is also more complicated. Older people typically have several medical conditions that need treatment and because of the number of medications they are potentially taking, they are at an increased risk of having a side effect to the treatment. Some people will continue to feel anxious even after treatment, which is known as treatment-resistant anxiety. In people of various ages, adding an antipsychotic drug to another drug has been found to lower anxiety. However, it is not known whether this treatment strategy is effective specifically in older people.

At this time, there is little research on treatment-resistant anxiety in older people, and no resource available that summarises the evidence for how effective the various treatments available are at treating resistant anxiety disorders in older people, or how the treatments compare against each other. The aim of this systematic review is 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 are to assess the adverse effects associated with the various treatments, and to identify gaps in the evidence available. The project team will search the literature for evidence around the effectiveness of treatments, and any side effects of treatment.

1. **Decision problem**

**Background**

Anxiety disorders are persistent conditions that affect people of all ages, and there is consensus that most disorders develop sometime between childhood and young adulthood.1 It was once thought that the frequency of occurrence of anxiety disorders declined with increasing age. However, recognition of the difficulties in differentiating symptoms of anxiety from physiological and physical changes arising from the ageing process (e.g., changes in sleep pattern), together with the 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. Many older people with an anxiety disorder also suffer from various comorbidities, which can further complicate diagnosis and worsen the long-term outcome of the disorder.2 Comorbidities often include other anxiety and mental disorders, of which depression is the most common among older people.3 Of older people with a diagnosis of an anxiety disorder, studies indicate that between 13% and 29.4% of people will also meet criteria for diagnosis of major depressive disorder. Physical comorbidities frequently include substance misuse, arthritis and gastrointestinal and respiratory disorders.4,5

Prevalence of anxiety disorders in older people exceeds that of late-life depression and cognitive dysfunction,6 with estimated rates of anxiety disorders ranging from 3.2% to 14.2% in people aged over 65 years.3 Prevalence is even higher in older 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% to 20% of older people experience symptoms of anxiety that, although debilitating, do not meet criteria for a psychiatric diagnosis.1 Although the prevalence of anxiety disorders in older people is high, it is estimated that less than 1% of people will develop an anxiety disorder after the age of 65.7 Most people with a primary anxiety disorder experienced onset of their condition before the age of 41 (90%), with 75% of people diagnosed with an anxiety disorder before the age of 21.8

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, fall, physical and functional disability, loneliness, and dependence on carers. Anxiety has a considerable detrimental effect on an older person’s quality of life.

The term “anxiety disorder” encompasses the conditions of generalised anxiety disorder (GAD), obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), social phobia (also known as social anxiety disorder), specific phobia, and panic disorder. Some psychological and physical symptoms of anxiety are common across the disorders. Difficulty concentrating, feelings of trepidation, stress and restlessness are typical psychological manifestations of anxiety, whereas fatigue, heart palpitations, and trembling are common physical symptoms experienced by people with anxiety. GAD is the most common anxiety disorder in older people, with a prevalence of 3.1% to 11.2%.1

In addition to the general symptoms, each anxiety disorder is associated with specific symptoms and triggers. Symptoms that distinguish one disorder from another are listed in Table 1.

*Table 1. Symptoms associated with the different anxiety disorders*

|  |  |
| --- | --- |
| **Anxiety disorder** | **Disorder-specific symptoms** |
| GAD | Constant worries and fears |
| OCD | Unwanted thoughts or behaviours that seem impossible to stop or control |
| PTSD | Extreme anxiety disorder that can occur in the aftermath of a traumatic or life-threatening event |
| 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 |
| Panic disorder | Repeated, unexpected panic attacks, as well as fear of experiencing another episode |
| Abbreviations used in table: GAD, generalised anxiety disorder; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder. | |

Treatments offered for an anxiety disorder are dependent on the underlying cause of anxiety. Although treatment strategies are tailored to treat the particular symptoms associated with an anxiety disorder, the core pathway outlined by the National Institute for Care and Health Excellence (NICE) is similar across the disorders. Fundamentally, treatment follows a stepped-care model,9 with initial steps involving the identification and assessment of the anxiety disorder. Providing the patient with information to understand their disorder and the treatment options available is proposed as an important component of treatment. 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 (SMD = –0.86, 95% CI –1.03 to –0.69 [20 studies, N = 1121]).10 It should be noted that the evidence is based on a synthesis of data from trials in various anxiety disorders and moderate statistical heterogeneity (44%) was present. Considered separately, the evidence base for the effectiveness of self-help in the individual anxiety disorders is limited.

If symptoms of anxiety persist, psychological interventions (e.g., individual guided self-help and psychoeducational groups) are typically offered. Treatments available to patients with an inadequate response to low-intensity psychological interventions are high-intensity psychological interventions, such as cognitive behavioural therapy (CBT) or applied relaxation, or a pharmacological therapy. The first choice for pharmacological treatment is usually an SSRI. Other options are serotonin–noradrenaline reuptake inhibitor (SNRI), pregabalin, or a benzodiazepine. Complex drug and/or psychological treatment, crisis services, day hospitals or inpatient care might be necessary for patients who do not respond to initial psychological or pharmacological treatment, those who are at high the risk of self-harm or neglect, and those suffering from substantial comorbidities.

Older people are more likely to consult their primary care physician because of somatic or general symptoms rather than concerns about their anxiety.11 As a result, pharmacotherapy for psychiatric symptoms is common in primary care, and many older people are prescribed benzodiazepines rather than an SSRI to manage their anxiety. Benzodiazepines have been associated with toxicity, dependence, abuse, cognitive impairment, and increased risk of falls in older people.12

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,3 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 number of drugs administered.8 Additionally, it is well recognised that compliance to treatment among older people is low. Lower tolerability for treatment and decline in cognitive function, which is a natural part of ageing, both contribute to the low rate of compliance.13 Poor compliance can exacerbate chronic medical conditions, and lead to increased reliance on carers, and, ultimately, admission to a residential facility.

As is seen with younger adults, the course of anxiety disorders in older people is cyclical in nature, but most disorders are unlikely to remit completely. In clinical trials involving a mixed-age population, remission rates of 20% to 47% have been reported.14 Treatment-resistant anxiety disorders have been the focus of numerous randomised controlled trials (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.14 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 has also been determined by no response after treatment with at least two antidepressants at adequate dose. Again, studies vary in the required duration of standard treatment. Categorisation of treatment resistance is further complicated by the nature of anxiety disorders. Avoidance of the object that triggers anxiety might lead to a reduction in severity of or resolution of symptoms, and, thus, any improvement is not necessarily as a result of response to treatment. Accordingly, continued presence of symptoms of anxiety after treatment does not necessarily indicate resistance or refractoriness to therapy but instead can suggest inadequate initial treatment or a natural transient reaction to a stress factor. 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.

One strategy for which there is a strong evidence base in treating resistant anxiety in a mixed-age population is augmentation of pharmacotherapy. In a review of the literature, Ipser and colleagues identified 28 RCTs evaluating addition of predominantly an antipsychotic to ongoing pharmacotherapy.15 Most RCTs evaluated short-term (average follow-up of 7 weeks) augmentation of an SSRI with an antipsychotic for the treatment of people not responding to first-line treatment for OCD. Although results suggest that augmentation can be effective in the short-term, methodological and clinical heterogeneity among trials preclude drawing definitive conclusions on effectiveness. As noted earlier, treatment of older people is typically complicated by issues such as polypharmacy and comorbidity, and results from a mixed-age sample cannot be extrapolated to an older population. 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.

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.

Despite the high prevalence of anxiety disorders in older people, few RCTs have been carried out in older people, with many RCTs excluding patients over the age of 55 years. Furthermore, although treatment-resistant anxiety is the focus of considerable research, few studies have focused on older people who do not respond to first-line treatment. The evidence base to direct treatment of resistant anxiety is limited and, therefore, current treatment strategies are not evidence-based. Guidance on the treatment of persistent anxiety in older people is also lacking. At this time, there is no resource that summarises the evidence for how effective the various available treatments are at improving symptoms of treatment-resistant anxiety in older people, or how the treatments compare against each other. The objectives of this systematic review are to:

* + - * Evaluate the clinical effectiveness of medical treatments for treatment-resistant anxiety in older people;
      * Evaluate the clinical effectiveness of psychological treatments for treatment-resistant anxiety in older people;
      * Identify key areas for further primary and secondary research.

Adverse effects associated with the various treatments will also be assessed and compared.

**Planned PICO criteria**

The planned criteria pertaining to population, intervention, comparators, and outcomes are summarised in Table 2. Based on a preliminary assessment of the literature on clinical effectiveness of treatments in older people with treatment-resistant or refractory anxiety, it is anticipated that a limited number of relevant RCTs will be identified, which is likely to necessitate inclusion of observational data in the review.

*Table 2. Planned PICO criteria*

|  |  |
| --- | --- |
| **PICO** | **Criteria** |
| Population | People aged ≥65 years with a primary diagnosis of an anxiety disorder and who are resistant/refractory to treatment. |
| Anxiety disorder | 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) will 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 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).  Should sufficient RCTs be identified, the decision might be taken to exclude observational data. |
| Other criteria | No restrictions on language or date of publication. |
| Abbreviations used in table: GAD, generalised anxiety disorder; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder; QoL, quality of life; RCTs, randomised controlled trials. | |

**Subgroup analyses**

Should sufficient data be identified to facilitate subgroup analyses, effects of interventions in the subgroups listed below will be considered separately:

* + - * baseline severity of anxiety based on validated disease-specific outcome measures (mild vs moderate vs severe);
      * comorbid psychiatric disorder (e.g., comorbid depression vs absence of depression);
      * alcohol misuse (yes vs no);
      * physical illness (yes vs no);
      * men vs women.

1. **Report methods for synthesis of evidence of clinical effectiveness**

A review of the evidence for clinical effectiveness will be undertaken systematically following the general principles recommended in the PRISMA statement (formerly the QUOROM statement).16 A flow diagram illustrating the flow of information through the systematic review process will be presented according to the PRISMA reporting guidelines.

**Search strategy**

The search strategy will comprise the listed main elements:

1. searching of electronic bibliographic databases;
2. contact with clinical experts in the field;
3. review of the reference lists of retrieved papers.

*Electronic searches*

The electronic databases that will be searched are:

* + - * MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (draft search strategy provided in Appendix 9.1);
      * EMBASE;
      * The Cochrane Library (specifically Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews and Effects, and Health Technology Assessment Database);
      * PsycINFO;
      * Web of Science(R).

Clinical trial registers will also be searched to identify relevant ongoing clinical trials that when completed may have an impact on the results of this review. Registers to be searched include:

* + - * WHO International Clinical Trials Registry Platform;
      * ClinicalTrials.gov (<http://clinicaltrials.gov/>).

*Contacting clinical experts*

Clinical experts, in addition to Professor David Baldwin, in the relevant therapy area will be contacted with a request for details of trials (published and unpublished) of which they may be aware. Experts will be allowed 28 days to provide an initial response, with any additional time allowed being dependent on whether the data analysis stage of the review has been reached.

*Review of the reference lists of retrieved papers*

The references from any relevant review papers or RCTs identified by the search will be examined for additional, potentially relevant references.

**Abstract appraisal**

Titles and abstracts of studies identified by the search process will be assessed independently by two reviewers for inclusion. In cases in which the reviewers are unable to reach a consensus as to whether the full text should be obtained for further appraisal, the full text will be obtained.

When potentially relevant data are available in only an abstract format, attempts will be made to contact the corresponding author to obtain the full publication. A deadline for response to the initial contact of 1 calendar month will be imposed. Additional time might be allowed should the author be able to supply the data requested. Information supplied after the deadline will potentially be included in only the discussion section of the report.

**Inclusion criteria**

For the review of clinical effectiveness, the preference will be to include only RCTs. However, it is anticipated that limited data will be available from RCTs. Should insufficient evidence from RCTs be identified, criteria will be relaxed and comparative observational studies (prospective matched control studies, case series and case control studies) will be included. Observational studies reporting on adverse effects of treatments in the population of interest will also be included.

Studies not meeting the PICO criteria outlined in the table above will be excluded. Studies will also be excluded if they are:

* + - * trials reporting only post-crossover results: study authors will be contacted to attempt to obtain pre-crossover results. If pre-crossover results cannot be obtained, the study will be excluded;
      * case reports, historical articles, narrative reviews, editorials, and opinion pieces;
      * reports published as only meeting abstracts, and where insufficient methodological details are reported to allow critical appraisal of study quality.

**Study inclusion assessment**

Two reviewers will independently assess the full text of the trials identified during the abstract assessment stage for inclusion and any differences in opinion will be arbitrated by a third reviewer. Studies rejected at this or subsequent stages will be recorded in a ‘characteristics of excluded studies table’, and reasons for exclusion recorded.

**Data extraction strategy**

A pragmatic decision for data extraction and validation will be made depending on the number of trials identified. Should 10 or fewer studies be identified as relevant for inclusion in the review, data will be extracted by two reviewers using a standardised data extraction form (draft form provided in Appendix 9.2). The data extraction form will be pilot tested on a sample of three studies and modified as required before use. Discrepancies in the data extracted by the two reviewers will be resolved through discussion, with involvement of a third reviewer if necessary. Should more than 10 studies be identified, data will be extracted by two reviewers for 10 studies, after which data will be extracted by one reviewer and validated by the second. Discrepancies will be resolved through discussion, with involvement of a third reviewer if necessary.

Data from intention-to-treat (ITT) analyses will be extracted: per protocol (PP) data will also be extracted for use in a sensitivity analysis. Should a trial not report ITT data, missing data will be treated as treatment failures to allow analysis to conform to an ITT analysis. For the purpose of this review, ITT is defined as analysis of patients in the treatment group to which they were allocated at randomisation, irrespective of whether they received the allocated intervention, withdrew, or were lost to follow-up.

Study authors will be contacted to supply any additional information not included in published sources, with a deadline of 1 calendar month for return of comments.

**Quality assessment strategy**

The quality of the outcome data from studies that meet the inclusion criteria will be assessed using the risk of bias tool developed by the Cochrane Collaboration.17 Two reviewers will independently rate the trial data for each outcome for inclusion and any differences in opinion will be arbitrated by a third reviewer. Outcome data from an RCT will be considered appropriate for inclusion unless the trial demonstrates some feature that necessitates the exclusion of that data. Seven domains will be assessed for each included study:

* + - * random sequence generation;
      * allocation concealment;
      * blinding of participants and personnel;
      * blinding of outcomes assessment;
      * incomplete outcome data;
      * selective reporting;
      * ‘other bias’ (includes any source of bias not captured by the other domains).

Each domain will be categorised as low risk, high risk or unclear risk of bias. Unclear risk is likely to be assigned due to poor reporting of trial conduct rather than a poorly conducted trial.18 For each outcome, a summary assessment of low risk of bias will be given when all key domains are judged to be at a low risk of bias, unclear risk of bias when there is an unclear risk of bias for one or more key domains, and high risk of bias when there is a high risk of bias for one or more key domains. Outcome data with a summary assessment of low or unclear risk of bias will be included in the main analysis and data rated high risk will be included in a sensitivity analysis. Across studies, a summary assessment of the risk of bias for the primary outcome (across domains) will be undertaken.17

**Methods of analysis/synthesis**

Data will be tabulated and discussed in a narrative review. Where appropriate, meta-analysis will be implemented to estimate a summary measure of effect on relevant outcomes based on ITT analyses. For dichotomous outcomes, odds ratio will be used as the summary statistic, and for continuous outcomes weighted mean difference will be the summary statistic. Meta-analyses will be conducted only if there are clinically homogeneous studies of similar comparisons reporting the same outcome measures. Standard pair-wise meta-analysis will be conducted when more than one trial is identified for inclusion for any pair of treatments under investigation. This will be carried out using a fixed effects model with the Mantel-Haenszel method.19 Sensitivity analysis will be conducted using a random effects model with the DerSimonian & Laird method.20 Subgroup analyses will be performed for the subgroups outlined in Section 4, should the evidence allow.

Should sufficient data be identified to facilitate a mixed treatment comparison (MTC), the MTC will be carried out based on a fixed effects and a random effects model with the most appropriate model identified as the one with the lowest deviance information criterion (DIC).21 For the chosen model, consistency of the evidence will be assessed using the posterior mean residual deviance, which should approximate the number of unconstrained data points in a good-fitting model.

**Heterogeneity**

For pair-wise meta-analysis, heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ2 test for homogeneity and the *I*2 statistic. Statistically significant heterogeneity will be defined as p <0.10. Levels of inconsistency will be assessed using *I*2 and will be defined as follows: *I*2 of: 0%–25% = low level of inconsistency; 26%–50% = moderate level of inconsistency; and >50% = high level of inconsistency.22

If statistically significant heterogeneity is detected in any of the analyses, hypothesis-generating subgroup analysis will be conducted, but the results from such analyses will be treated with caution. Meta-regression will be attempted if significant statistical heterogeneity is identified among trials analysed and there are 10 or more trials in the comparison.

For the MTC, where a random effects model is deemed the best fit, the degree of heterogeneity will be investigated by evaluating the posterior mean of tau-squared. Where possible, any closed loops formed by the network of trials will be assessed separately to determine if the results from the “direct” evidence is coherent with the “indirect” evidence when the wider network is introduced. Any incoherence identified will be investigated.

**Sensitivity analysis**

Sensitivity analyses will be carried out for aspects of the review that might have an impact on the results, for example, including studies identified as associated with a high risk of bias. Sensitivity analysis will be carried out for only the pre-specified primary outcomes.

**Publication bias**

For each of the primary pair-wise meta-analyses, a funnel plot will be used to assess publication bias. A regression of normalized effect versus precision will also be calculated as a test for small study effects (using a p <0.10 as an indicator of a significant result).23

1. **Expertise in this TAR team**

|  |  |
| --- | --- |
| **Name** | **Expertise** |
| Steve Edwardsa | Systematic reviewing, and economic evaluation and modelling |
| Charlotta Karnera | Systematic reviewing |
| Samantha Bartona | Systematic reviewing |
| Nicola Trevora | Systematic reviewing and economic evaluation |
| Elizabeth Thurgara | Systematic reviewing and economic evaluation |
| Fatima Saliha | Systematic reviewing and economic evaluation |
| David Baldwinb | Clinical expert |
| a BMJ-TAG, BMJ, BMA House.  b Faculty of Medicine, University of Southampton. | |

**About BMJ-TAG**

The BMJ-TAG is one of the Centres of Excellence identified by NIHR to undertake HTA. The BMJ-TAG is responsible for conducting independent Health Technology Assessments for the UK HTA Programme, in addition to systematic reviews and economic analyses for the National Institute for Health and Care Excellence. The BMJ-TAG comprises systematic reviewers and health economists with diverse experience of evidence-based health care.

**Recent publications**

Edwards SJ, Barton S, Thurgar E, Trevor N. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer: A Multiple Technology Appraisal. BMJ-TAG, London, 2013.

Edwards SJ, Barton S, Nherera L, Trevor N, Krause T, Thurgar E. Pixantrone monotherapy for the treatment of relapsed or refractory aggressive non-Hodgkin’s lymphoma: A Single Technology Appraisal. BMJ-TAG, London, 2013.

Edwards SJ, Karner C, Trevor N, Barton S, Nherera L. Mirabegron for the treatment of symptoms associated with overactive bladder. BMJ-TAG, London, 2013.

Edwards SJ, Hamilton V, Nherera L, Trevor N. Lithium or an atypical anti-psychotic in the management of treatment resistant depression: systematic review and economic evaluation. BMJ-TAG, London, 2012.

Edwards SJ, Barton S, Thurgar E, Nherera L, Hamilton V, Karner C, *et al*. Bevacizumab for the treatment of recurrent advanced ovarian cancer: A Single Technology Appraisal. BMJ-TAG, London, 2012.

1. **Competing interests of authors**

**Professor David S. Baldwin**

Professor Baldwin has received honoraria from Pfizer and Servier for speaking at conferences, consultancy fees from Lundbeck and Pfizer, and funding for research from Pfizer. He is Chair and an author of the British Association for Psychopharmacology evidence-based guidelines for the pharmacological treatment of anxiety disorders (published 2005, revision in preparation). He is responsible for organising responses from the European College of Neuropsychopharmacology to draft guidelines from the European Medicines Agency on the investigation of medicinal products.

1. **Timetable/milestones**

Send draft protocol to NETSCC, HTA: 16 August 2013

Send progress report to NETSCC, HTA: 16 November 2013

Submit assessment report to NETSCC, HTA: 16 December 2013

The timetable is based on a 3-month working time-frame, commencing in September 2013 and assuming that the final approval of the protocol has been received by this time.

1. **Appendices** 
   1. ***Draft MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) search strategy (from inception to 10 August 2013)***

1) exp Anxiety Disorders/ (66976)

2) ((anxi$ adj2 disorder) or (neuro$ adj2 worr$) or (neuro$ adj2 state$)).tw. (12833)

3) (obsess$ adj2 compuls$).tw. (11447)

4) ocd.ti,ab. (5731)

5) (post adj2 trauma$).tw. (20040)

6) ptsd.ti,ab. (12174)

7) (social adj2 (phobi$ or anxi$)).tw. (6518)

8) panic.ti,ab. (11695)

9) or/1-8 (97860)

10) exp Treatment Failure/ (27188)

11) (refract$ or resistan$ or nonrespon$ or non-respons$ or unrespon$ or fail$ or (incomplet$ adj respon$) or (no$ adj2 respon$)).tw. (1662387)

12) (inadequat$ respon$ or (sub$ adj2 respon$) or (poor$ adj respon$)).tw. (44157)

13) or/10-12 (1703377)

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. (2062470)

15) exp Adult/ (5545758)

16) exp Aged/ or exp Middle Aged/ or exp Retirement/ (3848677)

17) or/14-16 (6570916)

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)") (3845531)

19) case report.tw. (199487)

20) letter/ (817960)

21) historical article/ (297722)

22) or/19-21 (1303876)

23) 9 and 13 and 18 (2267)

24) 23 not 22 (2202)

* 1. ***Pilot data extraction form***

|  |  |
| --- | --- |
| **Item** | **Details** |
| ***Section 1: Reviewer and study information*** | |
| Reviewer name |  |
| Date of completion of form |  |
| Study ID |  |
| Study details (journal, year, volume, page range) |  |
| Language of publication |  |
| Type of report (full paper/only abstract/conference abstract) |  |
| ***Section 2: Verification of study eligibility (if the study does not meet any listed criteria do not proceed to Section 3)*** | |
| Type of study (RCT, prospective matched control study, case series, case control) |  |
| Population: people aged ≥65 years with a primary diagnosis of an anxiety disorder and who are resistant/refractory to treatment |  |
| Interventions: any intervention (psychological, pharmacological, or alternative) used to treat treatment-resistant anxiety either alone or in combination |  |
| Outcomes:  At least one of the listed outcomes evaluated:   * 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); * response; * remission; * functional disability; * sleep quality; * development of and change in symptoms of depression; * adherence to treatment; * QoL; * carer outcomes * adverse effects. |  |
| ***Section 3: study information*** | |
| Location and number of sites |  |
| Trial sponsor |  |
| Reported conflicts of interest |  |
| Patient enrolment (how and from where patients were recruited, and date to date of enrolment) |  |
| Trial design (e.g., RCT, cross-over RCT) |  |
| Inclusion criteria |  |
| Exclusion criteria |  |
| Outcomes reported |  |
| Subgroups evaluated |  |
| Stratification |  |
| Measure of anxiety at baseline |  |
| Ethnicity |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Treatment** | **Intervention [NAME]** | | | **Comparator [NAME]** | | | |
| Randomised, N |  | | |  | | | |
| Withdrawals (specify reasons for withdrawal), n (%) |  | | |  | | | |
| Treatment regimen (delivery, dose, and formulation) |  | | |  | | | |
| Treatment duration (length of treatment, with SD/SE if given) |  | | |  | | | |
| Treatment discontinuation |  | | |  | | | |
| Concomitant medications |  | | |  | | | |
| If the comparator was placebo, was the formulation and appearance matched to that of the other intervention? |  | | | | | | |
| Did both groups experience the same care except for the two interventions under investigation? |  | | | | | | |
| **Baseline patient characteristics** | | | | | | | |
| Age, years (range) |  | | |  | | | |
| Sex (n, %) |  | | |  | | | |
| Primary diagnosis of anxiety disorder, n (%) |  | | |  | | | |
| Age of onset of anxiety, years (range) |  | | |  | | | |
| Mean length of time since diagnosis of anxiety disorder, years |  | | |  | | | |
| Number of lines of previous treatment |  | | |  | | | |
| Classification of anxiety disorder (e.g., GAD, PTSD, social phobia), n (%) |  | | |  | | | |
| Comorbid diagnosis (e.g., depression, alcohol misuse, physical illness) |  | | |  | | | |
| ***Section 4: Outcomes*** | | | | | | | |
| *Outcome* | *Definition* | | | | | | |
| Reduction in symptoms of anxiety (as defined in the trial) |  | | | | | | |
| Response |  | | | | | | |
| Remission |  | | | | | | |
| Functional disability (trial scale used) |  | | | | | | |
| Sleep quality |  | | | | | | |
| Development of and change in symptoms of depression |  | | | | | | |
| Adherence to treatment |  | | | | | | |
| Quality of life (trial scale used) |  | | | | | | |
| Adverse events (please specify) |  | | | | | | |
| ***Section 5: ITT data extraction form*** | | | | | | | |
| **Outcome** | **Timeframe** | **Intervention** | | | **Comparator** | | **Estimate of effect (CI and p value)** |
|  |  | n | N | | n | N |  |
| Reduction in symptoms of anxiety |  |  |  | |  |  |  |
| Response |  |  |  | |  |  |  |
| Remission |  |  |  | |  |  |  |
| Functional disability |  |  |  | |  |  |  |
| Sleep quality |  |  |  | |  |  |  |
| Development of and change in symptoms of depression |  |  |  | |  |  |  |
| Adherence to treatment |  |  |  | |  |  |  |
| Quality of life |  |  |  | |  |  |  |
| Adverse events (please specify and use multiple rows) |  |  |  | |  |  |  |
| ***Section 6: Clinical trial quality*** | | | | | | | |
| Method of randomisation |  | | | | | | |
| Method of allocation concealment |  | | | | | | |
| Method of masking and who was masked |  | | | | | | |
| Number of patients lost to follow up (the overall number and number by treatment group, give reasons for loss to follow up) |  | | | | | | |
| ***Section 7: Additional comments*** | | | | | | | |
| Additional comments (e.g., power calculation, important changes to protocol, type of analysis) |  | | | | | | |
| Further information that could be requested from authors |  | | | | | | |
| Abbreviations used in table: CI, confidence interval; n, number of patients with the outcome; N, number of patients assessed; QoL, quality of life; RCT, randomised controlled trial; SD, standard deviation; SE, standard error. | | | | | | | |

**Risk of bias assessment for individual trials**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Risk of bias** | **Low risk** | **Unclear risk** | **High risk** | **Support for judgement** |
| ***Trial design*** | | | | | |
|  | 1. Random sequence generation |  |  |  |  |
|  | 1. Allocation concealment |  |  |  |  |
|  | 1. Selective reporting |  |  |  |  |
|  | 1. ‘Other Bias’ |  |  |  |  |
| ***Outcome-specific bias*** | | | | | |
| Reduction in symptoms of anxiety (as defined in the trial) | 1. Blinding (participants & personnel) |  |  |  |  |
| 1. Blinding of outcomes assessment |  |  |  |  |
| 1. Incomplete outcome data |  |  |  |  |
| Functional disability (trial scale used) | 1. Blinding (participants & personnel) |  |  |  |  |
| 1. Blinding of outcomes assessment |  |  |  |  |
| 1. Incomplete outcome data |  |  |  |  |
| Sleep quality | 1. Blinding (participants & personnel) |  |  |  |  |
| 1. Blinding of outcomes assessment |  |  |  |  |
| 1. Incomplete outcome data |  |  |  |  |
| Development of and change in symptoms of depression | 1. Blinding (participants & personnel) |  |  |  |  |
| 1. Blinding of outcomes assessment |  |  |  |  |
| 1. Incomplete outcome data |  |  |  |  |
| Adherence to treatment | 1. Blinding (participants & personnel) |  |  |  |  |
| 1. Blinding of outcomes assessment |  |  |  |  |
| 1. Incomplete outcome data |  |  |  |  |
| Quality of life (trial scale used) | 1. Blinding (participants & personnel) |  |  |  |  |
| 1. Blinding of outcomes assessment |  |  |  |  |
| 1. Incomplete outcome data |  |  |  |  |
| Adverse events | 1. Blinding (participants & personnel) |  |  |  |  |
| 1. Blinding of outcomes assessment |  |  |  |  |
| 1. Incomplete outcome data |  |  |  |  |
| **Overall rating of bias** | |  |  |  |  |

* 1. ***Contributions of team members***

|  |  |  |
| --- | --- | --- |
| **Name** | **Position** | **Contribution** |
| Steve Edwards | Head of Clinical and Economic Evidence, BMJ Clinical Improvement Division | Steve will contribute to the editing of the protocol and report. He will act as overall Director of the project and Guarantor of the report. |
| Charlotta Karner | Health Technology Assessment Analyst Lead | Charlotta will assess abstracts and titles for inclusion and exclusion and contribute to the clinical effectiveness review. It is intended that she will contribute to the editing of the protocol and writing and editing of the report. |
| Samantha Barton | Senior Health Technology Assessment Analyst | Sam has drafted the study protocol. She will draft and run the search strategies for the review of clinical effectiveness, and will assess abstracts and titles for inclusion and exclusion, and lead the systematic review of clinical effectiveness. It is intended that she will contribute to the writing and editing of the report and provide overall project management. |
| Nicola Trevor | Health Economist Lead | It is intended that Nicola will assess abstracts and titles for inclusion and exclusion, and contribute to the editing of the protocol and report. |
| Elizabeth Thurgar | Senior Health Economist | It is intended that Elizabeth will assess abstracts and titles for inclusion and exclusion, and contribute to the editing of the protocol and report. |
| Fatima Salih | Health Economist | It is intended that Fatima will assess abstracts and titles for inclusion and exclusion, and contribute to the editing of the protocol and report. |
| David Baldwin | Professor of Psychiatry  College Keep,  4–12 Terminus Terrace,  University of Southampton,  United Kingdom.  SO14 3DT. | David will provide clinical input throughout the project and will contribute to the editing of the protocol and report. |

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## Appendix 5. 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(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(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(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(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) |
| 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(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) |
| 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 et al.(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) |