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## Drug therapy for symptoms associated with anxiety in adult palliative care patients (Review)

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Drug therapy for symptoms associated with anxiety in adult palliative care patients.

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[Intervention Review]

# Drug therapy for symptoms associated with anxiety in adult palliative care patients

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## ABSTRACT

### Background

This is an update of a Cochrane Review first published in 2004 (Issue 1) and previously updated in 2012 (Issue 10). Anxiety is common in palliative care patients. It can be a natural response to the complex uncertainty of having a life-limiting illness or impending death, but it may represent a clinically significant issue in its own right.

### Objectives

To assess the effectiveness of drug therapy for treating symptoms of anxiety in adults with a progressive life-limiting illness who are thought to be in their last year of life.

### Search methods

We ran the searches for this update to May 2016. We searched the CENTRAL, MEDLINE (Ovid), Embase (Ovid), CINAHL (EBSCO), PsychLIT (Silver Platter) and PsycINFO (Ovid). We searched seven trials registers and seven pharmaceutical industry trials registers. We handsearched the conference abstracts of the European Association of Palliative Care.

### Selection criteria

Randomised controlled trials which examined the effect of drug therapy for the treatment of symptoms of anxiety in adult palliative care patients, that is, people with a known progressive life-limiting illness that is no longer responsive to curative treatment, including advanced heart, respiratory and neurological diseases (including dementia). Comparator treatments included placebo; another drug therapy or different dose schedule; or a non-drug intervention such as counselling, cognitive behaviour therapies or relaxation therapies.

### Data collection and analysis

Two review authors independently screened titles and abstracts to identify potentially relevant papers for inclusion in the review. We sought full-text reports for all papers retained at this stage and two reviews authors independently assessed these for inclusion in the review. We planned to assess risk of bias and extract data including information on adverse events. We planned to assess the evidence using GRADE and to create a 'Summary of findings' table.

## **Main results**

In this update, we identified 707 potentially relevant papers and of these we sought the full-text reports of 10 papers. On examination of these full-text reports, we excluded eight and two are awaiting classification as we have insufficient information to make a decision. Thus, in this update, we found no studies which met our inclusion criteria. For the original review, we identified, and then excluded, the full-text reports of six potentially relevant studies. For the 2012 update, we sought, and excluded, two full-text reports. Thus, we found no studies that assessed the effectiveness of drugs to treat symptoms of anxiety in palliative care patients.

## **Authors' conclusions**

There is a lack of evidence to draw a conclusion about the effectiveness of drug therapy for symptoms of anxiety in adult palliative care patients. To date, we have found no studies that meet the inclusion criteria for this review. We are awaiting further information for two studies which may be included in a future update. Randomised controlled trials which assess management of anxiety as a primary endpoint are required to establish the benefits and harms of drug therapy for the treatment of anxiety in palliative care.

## **PLAIN LANGUAGE SUMMARY**

### **Drugs to help reduce anxiety in people nearing the end of life due to illness**

#### **Review question**

We aimed to answer the question “how good are drugs at treating anxiety and worry in adults who have an illness which is getting worse and are in the last year of their life?”

#### **Background**

Anxiety or worry is a common problem for people who have an illness which is getting worse and are in the last year of their life. People may be anxious for many reasons. These reasons include being worried about pain and treatment, having to rely on other people to help them and having to face death. Anxiety can make it difficult for people to cope with their illness. Anxiety can make other problems worse and harder to manage, problems such as pain or feeling short of breath. For people who are nearing the end of their life due to illness, it is important to reduce their worry if possible. The use of some medicines may help to reduce anxiety. However, anxiety in people who are nearing the end of life has not been studied very much. People with anxiety often do not have their anxiety properly treated.

We searched for studies which looked at how good medicines were at reducing worry in adults nearing the end of their life. We were interested in studies that compared use of a medicine to no medicine, another medicine or a different dose of that medicine, or treatments such as talking to someone or relaxation therapy. We were interested in studies that measured anxiety. We were interested in trials designed to ensure that participants had an equal chance of receiving any of the treatments being tested in each trial. This review was first done in 2004 and updated in 2012. This is the second update. We searched to May 2016 for studies to include in this review.

#### **Key results**

We found no studies to include in this review. No studies were found for the original 2004 review or for the 2012 update. There is a lack of studies assessing the effect of drugs on reducing anxiety in adults who are nearing the end of their life. We found two relevant studies which may be included in a future update, but we need more information before we can make a judgement. Anxiety can have a big impact on how a person can cope with their illness, and we therefore need to know how to reduce their anxiety. Good-quality studies on how to reduce anxiety are needed.

## **Description of the condition**

This is the second update of the review “Drug therapy for anxiety

## **BACKGROUND**

in adult palliative care patients” originally published in Issue 1, 2004 (Jackson 2004) of the Cochrane Library and published as a first update in Issue 10, 2012 (Candy 2012).

Anxiety can be an intractable and crippling condition. It impacts on the person’s ability to cope emotionally and to function socially, and may make physical symptoms more difficult to manage (Spencer 2010). In the advanced stages of a progressive, life-limiting illness it may also manifest with concomitant depression and result in the person experiencing even greater difficulties (Mitchell 2011; Wilson 2007). The symptoms of anxiety include feelings of apprehension, fear, irritability and tension. Cognitively, anxiety manifests itself as excessive worry or difficulty concentrating. Behavioural symptoms involve avoidant or compulsive tendencies, and physical and somatic symptoms include diarrhoea, sweating, restlessness, fatigue, and insomnia. People may also present with more acute symptoms including palpitations, tachycardia, and shortness of breath (Thielking 2003). Anxiety is a term for a number of disorders, specifically generalised anxiety disorders (GAD), substance-induced anxiety, adjustment disorders, obsessive-compulsive disorders, specific phobias such as in response to medical interventions, panic disorders and post-traumatic stress disorder (DSM-5 2013). GAD and panic disorder were found in one study to be the most common anxiety disorders in advanced disease (Wilson 2007). The importance of a holistic approach to managing all symptoms including anxiety has been reaffirmed by frameworks around palliative and end of life care including Ambitions for Palliative and End of Life Care (National Palliative and End of Care 2015) and National Institute for Health and Care Excellence (NICE) guidance on end of life care (NICE 2011a).

In people with a progressive life-limiting illness, anxiety can be a natural reaction to the extraordinary psychological and physical challenges to be faced including the prognostic and treatment uncertainties often associated with the situation. The prevalence of symptoms of excessive anxiety is under researched, but it is one of the most common reasons for a psychiatric consultation in this patient group (Roth 2007). Anxiety can increase because of a broad range of concerns faced, such as how well symptoms will be managed, increasing dependency on other people, increased social isolation, confrontation with existential issues, and a growing inability to support and be with family and friends. Anxiety may also occur as the result of poorly controlled symptoms, such as pain, or the use of medications. Despite these known risks, anxiety in terminally ill people is underdiagnosed and undertreated, and is less extensively researched than depression (Kolva 2011; Wilson 2007).

One of the challenges in palliative care is to distinguish between excessive or maladaptive anxiety, and normal distress. There are numerous causes; in particular, it has been highly correlated with uncontrolled pain (Payne 1995). In addition, many studies looking at psychiatric states in people with a life-limiting diagnosis do not clearly separate their assessments of depression and anxiety states or define clearly their study populations with respect

to where a person is on their illness journey. This makes it more difficult to identify if anxiety is associated with specific stages in an illness journey, such as the palliative phase.

Anxiety may be a manifestation of a change in metabolic state such as hypoxia or hypoglycaemia, or in the dying phase (last 48 hours of life) as part of the result of multiple organ failure. Certain medications commonly used in caring for people near the end of life may produce symptoms that can be confused with anxiety, for example, akathisia or motor restlessness. These include phenothiazines (e.g. prochlorperazine), butyrophenones (e.g. haloperidol), methotrimeprazine and metoclopramide. Abrupt discontinuation of certain substances can also lead to withdrawal and precipitate an anxiety state, for instance alcohol, nicotine, anticonvulsants, benzodiazepines, clonidine, corticosteroids, opioids and sedative-hypnotics (Maguire 1993). Numerous other medications and substances have been associated with anxiety symptoms and, therefore, a thorough medication history should always precede changes in a drug therapy regimen (Jackson 2000).

## Description of the intervention

While there are clinical guidelines for the treatment of clinically significant anxiety (Baldwin 2005; NICE 2011b; NICE 2015), few are specific to palliative care where treatments may need to be different because of the added psychological and physical burden of living with a terminal disease (National Consensus Project 2009; NICE 2004; NICE 2015). Treatment in palliative care can include behavioural techniques, such as cognitive behavioural therapy (CBT) (Moorey 2009), and drug therapy. In deciding on treatment options, the clinician has to consider whether a person has both sufficient energy to engage with non-pharmacological interventions and the time needed to establish the benefit of such interventions. In deciding whether a pharmacological approach may be useful, the severity of the person’s symptoms and the degree to which they interfere with overall function and well-being are important factors to consider. In addition, the clinician needs to assess whether the person has compromised hepatic and renal function, and must also consider the potential adverse effects of the drug therapy. Short-acting benzodiazepines, such as lorazepam and oxazepam, are often the drugs of choice in terminally ill people (Breitbart 1996; Henderson 2006; Noyes 1998; Roth 2007). However, they may not be suitable for everyone because of adverse effects such as excessive sedation and confusion, which are associated with an increased risk of falls. Furthermore, if benzodiazepines are given for longer than a few weeks, there is the potential risk of physical dependency. The palliative care literature lists a variety of other potentially useful agents in the management of anxiety including antidepressants, buspirone, chlorpromazine, haloperidol, hydroxyzine, levomepromazine, ketamine and atypical antipsychotic drugs (e.g. olanzapine, risperidone) (Khojainova 2002; Mintzer 2001).

## How the intervention might work

This review explores the evidence for the effectiveness of drugs to treat anxiety in palliative care patients. These medications have a variety of mechanisms of action, including some drugs where the exact mechanism is unknown. Drug therapy for treatment of anxiety can be considered to work from two distinct approaches. The first is related to the mechanism of action at the level of neurotransmitters in the central nervous system. These include dopamine, gamma amino butyric acid (GABA), noradrenaline and serotonin.

The second approach is aimed at reducing the physical symptoms of anxiety that result from autonomic hyperactivity, such as tremors and palpitations. In some instances, it is these physical manifestations that worsen the cognitive aspects of anxiety, such as an inability to concentrate or sense of foreboding. The use of drugs such as beta-blockers, which slow the heart rate, may reduce or eliminate these physical manifestations and so reduce the overall impact of anxiety. The use of agents to treat physical manifestations may reduce or possibly eliminate the need for agents aimed at altering neurotransmitter systems.

## Why it is important to do this review

Anxiety is a distressing condition that is particularly common and troublesome for people dealing with the advanced stages of a life-limiting condition. Excessive anxiety can manifest itself as both physical and emotional symptoms and can reduce a person's ability to cope physically and mentally with the life-limiting condition. Drugs represent one way of allaying a person's anxiety, but choosing the most appropriate drug is dependent on the clinician having access to evidence reviewing the effectiveness of drugs for anxiety in people with life-limiting conditions. To our knowledge prior to the original review in 2004 there had been no systematic search of the international literature for evidence regarding the effectiveness of drug therapy for anxiety disorders in palliative care patients.

## OBJECTIVES

To assess the effectiveness of drug therapy for treating symptoms of anxiety in adults with a progressive life-limiting illness who are thought to be in their last year of life.

## METHODS

### Criteria for considering studies for this review

### Types of studies

Randomised controlled trials (RCTs).

### Types of participants

Adult palliative care patients (aged 18 years or older) whose symptoms of anxiety were described by the trial authors as beyond what could be seen as normal in this patient group. This could be captured as a score equivalent to clinically significant symptoms on a validated scale, such as the Hamilton Anxiety Rating Scale (HAM-A) ([Hamilton 1959](#)).

We included trials where anxiety was described as a disorder such as adjustment disorder, obsessive-compulsive disorder, phobia, panic disorder, post-traumatic stress disorder or GAD. We sought to verify that symptoms reported as clinically significant were measured using validated scales, and if the population was described as having an anxiety disorder (specifically GAD, substance-induced anxiety, adjustment disorders, obsessive-compulsive disorders, specific phobias such as in response to medical interventions, panic disorders and post-traumatic stress disorder) that it was defined using the International Classification of Disease (ICD) ([ICD-10 2010](#)) or the Diagnostic and Statistical Manual of Mental Disorders ([DSM-III 1980](#); [DSM-R 1987](#); [DSM-IV 1994](#); [DSM-IV-TR 2000](#); [DSM-5 2013](#)).

For the purposes of the review, we defined palliative care patients as people with a progressive, life-limiting illness, no longer responsive to disease-modifying treatments who were thought to be in the last year (or so) of life and were, or would be, eligible to receive palliative care. We did not include studies in which participants were in the last 24 to 48 hours of life. At this time, symptoms of anxiety may also be in part a manifestation of irreversible processes such as multiple organ failure, and treatment may differ from that considered in earlier phases of the disorder.

### Types of interventions

Interventions for anxiety included any type of drug therapy, for example, 5-HT<sub>3</sub> receptor antagonists, anxiolytic agents, antidepressive agents, antipsychotic and atypical antipsychotic agents, benzodiazepines, butyrophenones, phenothiazines, antihistamines, barbiturates, sedative hypnotics, antiepileptic drugs, ketamine and beta-blockers. We did not include any non-conventional drugs, such as herbal medicines.

Comparator treatments included placebo; another drug therapy or different dose schedule; or a non-drug intervention such as counselling, CBT or relaxation therapies.

### Types of outcome measures

#### Primary outcomes

- Anxiety: studies were eligible for inclusion if they reported anxiety measured using a validated scale which measures either anxiety alone or as a subscale. Examples of validated instruments include the following:

- Hamilton Anxiety Rating Scale (HAM-A) ([Hamilton 1959](#));
- Symptom Check List-90 (SCL-90) anxiety sub scale ([Derogatis 1983](#));
- Diagnostic Interview Schedule (DIS) ([Robins 1981](#));
- Affects Balance Scale (ABS) ([Bradburn 1969](#));
- Hospital Anxiety and Depression Scale (HADS) ([Zigmond 1983](#));
- Edmonton Symptom Assessment System (ESAS) ([Bruera 1991](#));
- Profile of Mood States ([Pollock 1979](#));
- Rotterdam Symptoms Checklist ([de Haes 1996](#));
- Palliative care Outcome Scale (or Patient Outcome Scale) ([Hearn 1999](#));
- Support Team Assessment Schedule (STAS) ([Higginson 1993](#));
- Beck Anxiety Inventory (BAI) ([Beck 1988](#));
- State-Trait Anxiety Inventory (STAI) ([Spielberger 1983](#)).

We reported anxiety outcomes assessed at one week.

### Secondary outcomes

- Depression measured using any validated scale either alone or as a subscale. Examples of validated instruments include:
  - Hospital Anxiety and Depression Scale (HADS) ([Zigmond 1983](#));
  - Beck Depression Inventory (BDI) ([Beck 1961](#)).
- Breathlessness measured using a validated scale. An example includes:
  - St George's Respiratory Questionnaire ([Jones 1991](#)).
- Insomnia measured using any validated scale. Examples include:
  - Insomnia Severity Index ([Bastien 2001](#));
  - Pittsburgh Sleep Quality Index ([Buysse 1989](#));
  - Athens Insomnia Scale ([Soldatos 2000](#)).
- Participants experiencing any adverse events, such as sedation or failure of treatment.
- Withdrawals due to lack of efficacy, adverse events or any cause.

### Search methods for identification of studies

#### Electronic searches

To identify studies for inclusion in this review, we developed detailed search strategies for each electronic database searched. These were based on the search strategy developed for MEDLINE but revised appropriately for each database. The search strategy used in the original review run in 2003 is reported in [Appendix 1](#) and the search strategies used in the first update of 2012 are presented in [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), [Appendix 5](#), [Appendix 6](#), and [Appendix 7](#). The search strategies used in 2016 for the second update of this review are reported in [Appendix 8](#). We also updated the list of drugs included in the search and re-ran the search for these for all years to May 2016 (see [Appendix 9](#)).

#### Databases searched

- The Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 4) (Cochrane Register of Studies Online) (18 May 2016).
- MEDLINE (OVID) (1966 to May week 1 2016).
- Embase (OVID) (1980 to 16 May 2016).
- CINAHL (EBSCO) (1982 to 18 May 2016).
- PsychLIT (Silver Platter) (1974 to 2000).
- PsycINFO (OVID) (1990 to May week 2 2016).

For the original review, the Cochrane Pain, Palliative & Supportive Care Register was searched to July 2003 but its contents are now captured by CENTRAL and so we did not search it for this update.

#### Searching other resources

We searched the following trials and pharmaceutical industry trials registers.

#### Trials registers searched

- ClinicalTrials.gov ([clinicaltrials.gov/](#)) (to May 2016).
- metaRegister of controlled trials ([www.isrctn.com/page/mrct](#)) (to May 2016).
- ISRCTN Trials Register ([www.controlled-trials.com/isrctn](#)) (to 2012).
- Netherlands Trial Register ([www.trialregister.nl/trialreg/index.asp](#)) (to May 2016).
- NIHR Clinical Research Portfolio Database ([public.ukcrn.org.uk/search/](#)) (to May 2016).
- UMIN Japan Trial Register ([www.umin.ac.jp/ctr](#)) (to May 2016).
- UK Clinical Trials Gateway ([www.ukctg.nihr.ac.uk/default.aspx](#)) (to May 2016).
- World Health Organization (WHO) Portal (covers ClinicalTrials.gov; ISRCTN; Australian and New Zealand Clinical Trial Registry; Chinese Clinical Trial Register; India Clinical Trials Registry; German Clinical Trials Register; Iranian Registry of Clinical Trials; Sri Lanka Clinical Trials Registry; The

Netherlands National trial Register) ([www.who.int/trialsearch](http://www.who.int/trialsearch)) (to May 2016).

For the original review and the first update, we searched the ISRCTN Trials Register ([www.controlled-trials.com/isrctn](http://www.controlled-trials.com/isrctn)) to 2012, but its contents are captured by the WHO Portal and so we did not search it for this second update in 2017.

#### Pharmaceutical industry trials registers searched

- AstraZeneca Clinical Trials ([www.astrazenecaclinicaltrials.com](http://www.astrazenecaclinicaltrials.com)) (to May 2016).
- Daiichi Sankyo ([www.daiichisankyo.com](http://www.daiichisankyo.com)) (to May 2016).
- Eisai ([www.eisai.com/](http://www.eisai.com/)) (to May 2016).
- GlaxoSmithKline Clinical Trial Register ([www.gsk-clinicalstudyregister.com](http://www.gsk-clinicalstudyregister.com)) (to May 2016).
- Lundbeck ([www.lundbeck.com](http://www.lundbeck.com)) (to May 2016).
- NovartisClinicalTrials.com ([www.novartis.com/](http://www.novartis.com/)) (to May 2016).
- Roche Clinical Trial Protocol Registry ([www.roche-trials.com/main.action](http://www.roche-trials.com/main.action)) (to May 2016).

#### Conference abstracts

For this second update of the review, we handsearched the following conference abstracts:

- World Research Congress EAPC (2012 and 2014);
- World Congress EAPC (2013 and 2015).

We did not search the EAPC 2016 conference abstracts as the conference was not held until June 2016.

#### Reference lists

We searched the reference lists of review articles.

#### Unpublished data

We did not seek unpublished studies.

#### Language

The search was not restricted by language of publication.

### Data collection and analysis

#### Selection of studies

In this update, two review authors (SS and CM) independently assessed titles and abstracts for eligibility for inclusion in the review. We sought full-text reports of all potentially relevant studies remaining after the initial assessment and two review authors

(SS and CM) independently assessed these against our predefined inclusion criteria. We resolved any disagreements between the review authors by consulting a third review author (NP). Where we identified posters or conference abstracts which we considered potentially relevant, we sought full-text reports of the study and, if unsuccessful, we contacted study authors to seek further information. Where English translations for studies published in another language were not available at the screening stage, we obtained full-text reports and translated these initially using an electronic translator. We reported reasons for excluding full-text reports. See [Characteristics of excluded studies](#) table.

#### Data extraction and management

We designed a data extraction form to collect the following data:

- publication details;
- study eligibility criteria;
- study details (e.g. aim, start and end date, ethics approval);
- participant characteristics (e.g. number of participants, age, sex, diagnosis of anxiety, study setting);
- description of intervention and comparator (e.g. duration of treatment, timing, delivery, number randomised to groups);
- outcome details (e.g. instrument used to evaluate anxiety, time points when outcomes were assessed, withdrawals).

#### Assessment of risk of bias in included studies

We planned for two review authors (SS and CM) to independently assess risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), with any disagreements resolved by discussion. We planned to complete a 'Risk of bias' table for each included study using the 'Risk of bias' tool in Review Manager 5 ([RevMan 2014](#)).

We aimed to assess the following for each study.

- Random sequence generation (checking for possible selection bias). We planned to assess the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We planned to exclude studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number).

- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment. We planned to assess the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). We aimed to exclude studies that did not conceal allocation (e.g. open list).

- Blinding of participants and personnel (checking for possible performance bias). We planned to assess the methods

used to blind study participants and personnel from knowledge of which intervention a participant received. We aimed to assess methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, such as identical tablets matched in appearance or smell, or a double-dummy technique); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how it was achieved). Studies that were not double-blind were considered to have high risk of bias.

- Blinding of outcome assessment (checking for possible detection bias). We aimed to assess the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We planned to assess the methods as: low risk of bias (study had a clear statement that outcome assessors were unaware of treatment allocation, and ideally described how this was achieved); unclear risk of bias (study stated that outcome assessors were blind to treatment allocation but lacked a clear statement on how it was achieved). We considered studies where outcome assessment was not blinded as having a high risk of bias.

- Selective reporting (checking for reporting bias). We aimed to assess whether primary and secondary outcome measures were prespecified and whether these were consistent with those reported. We aimed to assess selective reporting as: low risk of bias (studies reported primary and secondary outcomes); high risk of bias (not all prespecified outcomes reported or only for certain data collection time points).

- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We planned to assess the methods used to deal with incomplete data as: low risk of bias (less than 10% of participants did not complete the study or used 'baseline observation carried forward' analysis), or both; unclear risk of bias (used 'last observation carried forward' analysis); high risk of bias (used 'completer' analysis).

- Size of study (checking for possible biases confounded by small size). We aimed to assess studies as being at low risk of bias (200 participants or greater per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (fewer than 50 participants per treatment arm)

### Measures of treatment effect

We planned to analyse dichotomous data as odds ratios and 95% confidence intervals (CI) and continuous data as mean difference and 95% CI.

### Unit of analysis issues

For any RCTs using a cross-over design, we planned to use only data from the first comparative phase prior to cross-over. This decision was based on the possibility of a carry-over of treatment effect from the drug evaluation or a comparative treatment.

### Dealing with missing data

For this review, we expected a significant loss to follow-up due to participants' declining health. We planned to report trial attrition rates in the 'Risk of bias' table. This would have included, if available, reasons for attrition per treatment arm. Where study data were missing but might have been available, we planned to contact the authors to obtain missing outcome data where possible. We planned not to exclude trials on the basis of missing data.

### Assessment of heterogeneity

If meta-analysis had been possible, we planned to use the  $I^2$  statistic to assess heterogeneity among the trials in each analysis. If we identified substantial heterogeneity (i.e.  $I^2$  greater than 50%), we aimed to report it and explore possible causes by performing prespecified subgroup analysis.

### Assessment of reporting biases

If meta-analysis had been possible using 10 or more studies, we planned to explore publication bias using Egger's test and by inspection of funnel plots for symmetry.

### Data synthesis

We planned to combine study data to provide a pooled effect estimate using a fixed-effect model. If we had found no substantial heterogeneity, we planned to use a random-effects model to check the robustness of the fixed-effect model. If substantial statistical heterogeneity had been observed, we would have used the random-effects model a priori.

If we had found studies that reported a mixture of change-from-baseline and final value scores, we would have only combined data if the studies reported the outcome using the same measurement scale.

Where there were insufficient studies to undertake a meta-analysis, we planned to combine individual studies in a narrative review.

### Quality of the evidence

We planned that two review authors (SS and CM) would independently rate the quality of the outcomes. We planned to use the GRADE system to rank the quality of the evidence using the GRADEprofiler Guideline Development Tool software ([GRADEpro GDT 2015](#)), and the guidelines provided in Section 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The GRADE system uses the following criteria for assigning grade of evidence:

- high: we are very confident that the true effect lies close to that of the estimate of the effect;
- moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
- low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
- very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We planned to decrease the grade rating by one (-1) or two (-2) if we identified:

- serious (-1) or very serious (-2) limitation to study quality;
- important inconsistency (-1);
- some (-1) or major (-2) uncertainty about directness;
- imprecise or sparse data (-1);
- high probability of reporting bias (-1).

#### 'Summary of findings' table

We planned to include six 'Summary of findings' tables to present the main findings for the primary outcome (anxiety) and five secondary outcomes (depression, breathlessness, insomnia, adverse events and withdrawals) in a transparent and simple tabular format. In particular, we planned to include key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data.

#### Subgroup analysis and investigation of heterogeneity

If three or more studies reported relevant data, we planned to perform the following subgroup analyses:

- men versus women;
- mild or moderate anxiety versus severe anxiety;
- follow-up no greater than one month versus follow-up greater than one month.

#### Sensitivity analysis

We planned to perform sensitivity analyses to explore the influence of the following factors:

- excluding unpublished studies;
- excluding studies considered at high risk of selection bias in terms of adequate allocation concealment, detection bias in terms of blinded outcome assessment and attrition bias due to follow-up of less than 80% of participants in each arm;
- excluding studies using the following filters:
  - industry funded;
  - non-validated scales used for measuring effect;
  - non-validated diagnostic criteria.

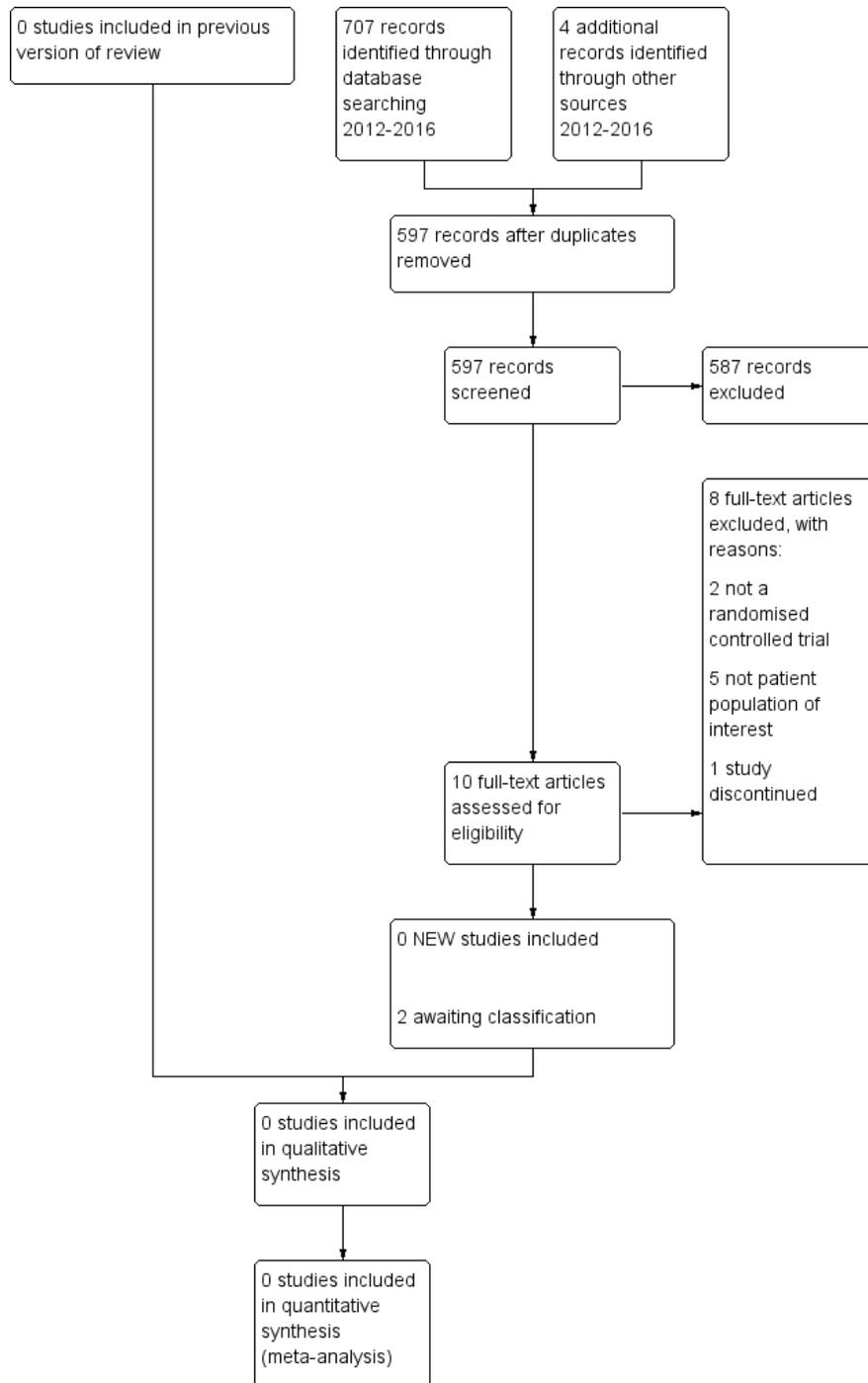
## RESULTS

### Description of studies

#### Results of the search

We retrieved 707 potentially relevant studies from the electronic searches and four from other sources for this second update. After removing duplicates, we screened 597 articles for inclusion in the review. We assessed full-text reports of 10 articles. [Figure 1](#) shows the results of the search.

**Figure 1. Study flow diagram.**



### Included studies

Of the 10 full-text reports we assessed for inclusion in this update, we did not identify any studies fulfilling our criteria.

### Excluded studies

In this update, we excluded eight reports for the following reasons: five did not include a patient population of interest, specifically it was considered that three included participants with depression and not anxiety (Centeno 2012; Dauchy 2015; Ng 2014), and two included participants not considered at a palliative stage of disease (Kronish 2012; Yazici 2012); two were not an RCT (Grob 2011; Irwin 2013), and one study was discontinued (Daubert 2014). See [Characteristics of excluded studies](#) table. Overall, there are 16 excluded studies.

### Studies awaiting classification

Two studies provided insufficient information on which to make a decision regarding inclusion, despite attempts to contact the authors for further information (Hart 2012; Usmani 2013).

### Ongoing studies

We did not identify any ongoing studies.

### Risk of bias in included studies

We did not identify any relevant studies.

### Effects of interventions

We did not identify any relevant studies.

## DISCUSSION

### Summary of main results

We found no studies assessing the effectiveness of drug therapy for treating symptoms of anxiety in adults with a progressive life-limiting illness and who were thought to be in their last year of life. There was a lack of RCTs; while we identified five RCTs, three studies assessed depression rather than anxiety and were thus excluded. There are two studies awaiting classification which may be included in a future update.

### Overall completeness and applicability of evidence

We were unable to find any evidence of the effectiveness of drug therapy in the treatment of adult palliative care patients experiencing symptoms of anxiety.

### Quality of the evidence

We did not identify any studies to include in the review and thus we are unable to assess the quality of the evidence.

### Potential biases in the review process

We undertook a comprehensive search for studies, including searching trials registers and handsearching of conference abstracts with no restrictions on language of study reports. One potential problem we encountered with identifying papers for inclusion was that when first reading a paper the title and abstract might suggest that the study participants were experiencing with anxiety but, on closer inspection, participants were assessed using scales which predominantly measured depression and thus studies did not meet our inclusion criteria.

### Agreements and disagreements with other studies or reviews

One systematic review of anxiety therapy for palliative care patients with cancer was undertaken at a similar time to the first update of this Cochrane Review (Nübling 2012). Nübling 2012 included four RCTs in their review but stated that they did not make recommendations for pharmacological treatments based on the findings of these four studies because of “deficiencies in the studies or the analyses.” All four studies were excluded from the original Cochrane Review of 2004 as study participants were not considered those of interest for this review. Traeger 2012 examined the evidence for treatment of anxiety in people with cancer and identified two of the studies included in the Nübling 2012 review. Traeger 2012 concluded that finding evidence for effective treatments of anxiety in people with cancer is challenging as anxiety is a complex problem, thus making a diagnosis of anxiety and assessing the effects of treatment is difficult.

## AUTHORS' CONCLUSIONS

## Implications for practice

Due to the lack of evidence on the role of drug therapy for treating anxiety in palliative care patients, this review cannot draw any conclusions specific to any medications or drug classes in this patient population. To the best of our knowledge, clinical guidelines from the main health organisations across the world recommend non-drug therapy treatments for anxiety in palliative care patients such as psychological support and intervention (NICE 2004), in preference to drug treatment except in the last days of life (NICE 2015). In the case of severe anxiety, guidelines recommend referral to a psychiatrist (National Consensus Project 2009). In addition, there is evidence for the effectiveness of cognitive behavioural therapy as a psychological intervention (Moorey 2009).

Until there is evidence indicating harms caused by the drugs currently used in palliative care to manage anxiety, their use is likely to be continued. However, their administration should be based on the severity of symptoms and an assessment of the risk of increased sensitivity to drugs. As addressed in the review, underlying causes for anxiety should be thoroughly evaluated to determine if the cause of a person's anxiety is related to other symptom management or the use of other medications or substances. If appropriate, treating another symptom (e.g. pain) or eliminating an agent that is causing or exacerbating anxiety (e.g. caffeine) may pre-empt the need for another medication to treat anxiety. If drugs are started, they should be at a lower dose than would be prescribed for physically healthy people and any increase should be attempted cautiously and with consideration of other drugs the person may be taking (Roth 2007). The drug group of choice commonly stated in the literature for palliative care patients (prior to the final dying phase) is short-acting benzodiazepines, such as lorazepam or midazolam (Henderson 2006; Klein 2011; Roth 2007).

## Implications for research

### General implications

As there is a lack of evidence of the effectiveness of drug therapy for treating anxiety in people with a life-limiting illness there is a need for research in this topic.

### Design

Randomised controlled trials (RCTs), adequately powered and involving more than 200 participants per arm are needed.

### Measurement (endpoints)

Depression and anxiety are often measured using the same scale, thus it is necessary that future trials specifically assess and report measures of anxiety. The diagnosis of anxiety should be clearly defined and be a discrete endpoint for the trial. Outcomes need to be assessed using validated tools.

### Other

RCTs should follow the CONSORT Statement (Schulz 2010).

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
<a href="#">Barreto 1996</a>	Not an RCT.
<a href="#">Bruera 1986</a>	Not the patient population of interest.
<a href="#">Butters 1992</a>	Not an RCT
<a href="#">Centeno 2012</a>	Not the patient population of interest.
<a href="#">Daubert 2014</a>	Study discontinued.
<a href="#">Dauchy 2015</a>	Not the patient population of interest.
<a href="#">Fernandez 1987</a>	Not an RCT.
<a href="#">Grob 2011</a>	Not an RCT.
<a href="#">Holland 1991</a>	Not the patient population of interest.
<a href="#">Irwin 2013</a>	Not an RCT.
<a href="#">Koralewski 2002</a>	Not the patient population of interest.
<a href="#">Kronish 2012</a>	Not the patient population of interest.
<a href="#">Ng 2014</a>	Not the patient population of interest.
<a href="#">Wald 1993</a>	Not the patient population of interest.
<a href="#">Yazici 2012</a>	Not the patient population of interest.
<a href="#">Ziolko 2004</a>	Not the patient population of interest.

RCT: randomised controlled trial.

## Characteristics of studies awaiting assessment *[ordered by study ID]*

### Hart 2012

Methods	Randomised, double-blind, double-dummy placebo-controlled pilot study
Participants	30 participants with severe respiratory disease.
Interventions	Lorazepam tablets 0.5 mg twice daily with dummy nasal spray up to 4 times daily Midazolam 400 mg intranasal 2 sprays up to 4 times daily with placebo tablets
Outcomes	Borg score, St Georges Respiratory Questionnaire, Hospital Anxiety and Depression scores, Nottingham Activities of Daily Living score
Notes	Contacted author by e-mail in July and August 2016 to ask for further details but no response received

### Usmani 2013

Methods	Intervention study.
Participants	People with chronic obstructive pulmonary disease.
Interventions	Paroxetine 20 mg daily as oral capsule for 4 months. Placebo pill as oral capsule for 4 months. Capsules identical in appearance.
Outcomes	Anxiety as measured by Beck Anxiety Inventory, quality of life as assessed by Chronic Respiratory Questionnaire (CRQ)
Notes	Contacted author by e-mail September 2016 to ask for further details but no response received

## DATA AND ANALYSES

This review has no analyses.

## APPENDICES

### Appendix 1. Search strategy used in 2003

The search strategy combined the subject search with phases 1 and 2 of the Cochrane Sensitive Search Strategy for RCTs (as published in Appendix 5c in the *Cochrane Handbook for Systematic Reviews of Interventions*).

The subject search used a combination of controlled vocabulary and free-text terms in addition to the basic Cochrane Sensitive Search Strategy. These terms included the following:

Disease: anxiety, agitation, adjustment disorders, obsessive-compulsive disorders, phobias, panic disorders, post-traumatic stress disorder, generalised anxiety disorders and terminal restlessness.

Individual treatments: alprazolam, bromazepam, chlordiazepoxide, clobazam, clonazepam, chlorazepate, diazepam, estazolam, flunitrazepam, flurazepam, halazepam, ketazolam, lorazepam, midazolam, nitrazepam, oxazepam, prazepam, quazepam, temazepam, triazolam, buspirone, hydroxyzine, amitriptyline, nortriptyline, desipramine, doxepin, fluoxetine, paroxetine, sertraline, citalopram, venlafaxine, droperidol, haloperidol, chlorpromazine, olanzapine, risperidone, thioridazine, methotrimeprazine and propofol.

Drug class names: anxiolytics, antidepressants, antipsychotics, benzodiazepines, butyrophenones, phenothiazines and thienobenzodiazepine.

### Appendix 2. MEDLINE search 2012

MEDLINE Ovid

1 exp Anxiety/

2 exp Anxiety Disorders/

3 Adjustment Disorders/

4 Psychomotor Agitation/

5 (anxious\* or anxiet\* or agitat\* or restless\* or panic\* or stress\* or PTSD or phobia\* or phobic or nervous\* or obsessive compulsive disorder\* or OCD or adjustment disorder\*).mp.

6 1 or 2 or 3 or 4 or 5

7 drug therapy.fs.

8 exp Anti-Anxiety Agents/

9 exp Antidepressive Agents/

10 exp Antipsychotic Agents/

11 exp Benzodiazepines/

12 exp Butyrophenones/

13 exp Phenothiazines/

14 exp Monoamine Oxidase Inhibitors/

15 exp Serotonin Agents/

16 exp Histamine Agents/

17 exp Barbiturates/

18 exp "Hypnotics and Sedatives"/

19 exp Adrenergic Agents/

20 (acebutolol or alimemazine or alprazolam or amitriptyline or atenolol or bisoprolol or bromazepam or bupropion or buspirone or carbamazepine or carisoprodol or carvedilol or celirolol or clomipramine or chlorazepate or chlordiazepoxide or chlorphenamine or chlorpromazine or citalopram or clemastine or clobazam or clonazepam or co-tenidone or cyproheptadine or diazepam or desipramine

or desvenlafaxine or dexmedetomidine or dosulepin or doxepin or droperidol or duloxetine or escitalopram or esmolol or estazolam or eszopiclone or etizolam or flunitrazepam or fluoxetine or flurazepam or fluvoxamine or gabapentin or halazepam or haloperidol or hydroxyzine or imipramine or isocarboxazid or ketamine or ketazolam or ketotifen or labetalol or lamotrigine or levetiracetam or levomepromazine or lofepramine or lorazepam or meprobamate or methotrimeprazine or metoprolol or midazolam or milnacipran or mirtazapine or moclobemide or nadolol or nebivolol or nefazodone or nitrazepam or nortriptyline or olanzapine or ondansetron or oxazepam or oxprenolol or paroxetine or perphenazine or phenelzine or phenobarbital or phenytoin or pindolol or prazepam or pregabalin or primidone or promethazine or propofol or propranolol or quazepam or ramelteon or risperidone or sertraline or sotalol or temazepam or thioridazine or tiagabine or timolol or topiramate or tranlycypromine or trazodone or triazolam or trifluoperazine or trimipramine or tropisetron or valproate or venlafaxine or vigabatrin or zaleplon or zolpidem).mp.

21 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22 Palliative Care/

23 exp Terminal Care/

24 Terminally Ill/

25 palliat\*.mp.

26 (terminal\* adj6 (care or ill\* or diseas\*)).mp.

27 (terminal-stage\* or terminal stage\* or dying or (close adj3 death)).mp.

28 (end adj3 life).mp.

29 hospice\*.mp.

30 ((end-stage\* or end stage\*) adj6 (disease\* or illness\* or care)).mp.

31 (incurable adj6 (disease\* or illness\*)).mp.

32 (advanced adj6 disease\*).mp.

33 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32

34 6 and 21 and 33

35 randomized controlled trial.pt.

36 controlled clinical trial.pt.

37 randomized.ab.

38 placebo.ab.

39 drug therapy.fs.

40 randomly.ab.

41 trial.ab.

42 groups.ab.

43 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42

44 34 and 43

key:

mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier

pt=publication type

ab=abstract

fs=floating subheading

### Appendix 3. CENTRAL search 2012

#1 MeSH descriptor Anxiety explode all trees

#2 MeSH descriptor Anxiety Disorders explode all trees

#3 MeSH descriptor Adjustment Disorders, this term only

#4 MeSH descriptor Psychomotor Agitation, this term only

#5 (anxious\* or anxiet\* or agitat\* or restless\* or panic\* or stress\* or PTSD or phobia\* or phobic or nervous\* or obsessive compulsive disorder\* or OCD or adjustment disorder\*)

#6 (#1 OR #2 OR #3 OR #4 OR #5)

#7 [Any MeSH descriptor with qualifier: DT](#)

#8 MeSH descriptor Anti-Anxiety Agents explode all trees

#9 MeSH descriptor Antidepressive Agents explode all trees

- #10 MeSH descriptor Antipsychotic Agents explode all trees
- #11 MeSH descriptor Benzodiazepines explode all trees
- #12 [MeSH descriptor Butyrophenones explode all trees](#)
- #13 MeSH descriptor Phenothiazines explode all trees
- #14 [MeSH descriptor Monoamine Oxidase Inhibitors explode all trees](#)
- #15 MeSH descriptor Serotonin Agents explode all trees
- #16 MeSH descriptor Histamine Agents explode all trees
- #17 MeSH descriptor Barbiturates explode all trees
- #18 [MeSH descriptor Hypnotics and Sedatives explode all trees](#)
- #19 MeSH descriptor Adrenergic Agents explode all trees
- #20 acebutolol or alimemazine or alprazolam or amitriptyline or atenolol or bisoprolol or bromazepam or bupropion or buspirone or carbamazepine or carisoprodol or carvedilol or celiprolol or clomipramine or chlorazepate or chlordiazepoxide or chlorphenamine or chlopropazine or citalopram or clemastine or clobazam or clonazepam or co-tenidone or cypripheptadine or diazepam or desipramine or desvenlafaxine or dexmedetomidine or dosulepin or doxepin or droperidol or doloxetin
- #21 escitalopram or esmolol or estazolam or eszopiclone or etizolam or flunitrazepam or fluoxetine or flurazepam or fluvoxamine or gabapentin or halazepam or haloperidol or hydroxyzine or imipramine or isocarboxazid or ketamine or ketazolam or ketotifen or labetalol or lamotrigine or levetiracetam or levomepromazine or lofepramine or lorazepam or meprobamate or methotrimeprazine or metoprolol or midazolam or milnacipran or mirtazapine or moclobemide or nadolol or nebivolol or nefazodone or nitrazepam or nortriptyline or olanzapine or ondansetron or oxazepam or oxprenolol or paroxetine or perphenazine or phenelzine or phenobarbital or phenytoin or pindolol or prazepam or pregabalin or primidone or promethazine or propofol or propranolol or quazepam or ramelteon or risperidone or sertraline or sotalol or temazepam or thioridazine or tiagabine or timolol or topiramate or tranlycypromine or trazodone or triazolam or trifluoperazine or trimipramine or tropisetron or valproate or venlafaxine or vigabatrin or zaleplon or zolpidem
- #22 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21)
- #23 MeSH descriptor Palliative Care, this term only
- #24 MeSH descriptor Terminal Care explode all trees
- #25 MeSH descriptor Terminally Ill, this term only
- #26 palliat\*
- #27 [terminal\\* near/6 \(care or ill\\* or disease\\*\)](#)
- #28 end near/6 life
- #29 hospice\*
- #30 (end -stage\* or end stage\*) near/6 (disease\* or illness\* or care)
- #31 incurable near/6 (disease\* or illness\*)
- #32 advanced near/6 disease\*
- #33 [terminal-stage\\* or terminal stage\\* or dying or \(close near/6 death\)](#)
- #34 (#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33)
- #35 (#6 AND #22 AND #34)

## Appendix 4. Embase search 2012

Embase Ovid

1 anxiety/

2 exp anxiety disorder/

3 adjustment disorder/

4 agitation/

5 (anxious\* or anxiet\* or agitat\* or restless\* or panic\* or stress\* or PTSD or phobia\* or phobic or nervous\* or obsessive compulsive disorder\* or OCD or adjustment disorder\*).mp.

6 1 or 2 or 3 or 4 or 5

7 dt.fs.

8 exp anxiolytic agent/

9 exp antidepressant agent/

10 exp neuroleptic agent/

11 exp benzodiazepine derivative/

12 exp butyrophenone derivative/  
13 exp phenothiazine derivative/  
14 exp serotonin receptor affecting agent/  
15 exp histaminergic receptor affecting agent/  
16 exp barbituric acid derivative/  
17 exp hypnotic sedative agent/  
18 beta adrenergic receptor blocking agent/ or exp adrenergic receptor blocking agent/  
19 (acebutolol or alimemazine or alprazolam or amitriptyline or atenolol or bisoprolol or bromazepam or bupropion or buspirone or carbamazepine or carisoprodol or carvedilol or celiprolol or clomipramine or chlorazepate or chlordiazepoxide or chlorphenamine or chlorpromazine or citalopram or clemastine or clobazam or clonazepam or co-tenidone or cyproheptadine or diazepam or desipramine or desvenlafaxine or dexmedetomidine or dosulepin or doxepin or droperidol or duloxetine or escitalopram or esmolol or estazolam or eszopiclone or etizolam or flunitrazepam or fluoxetine or flurazepam or fluvoxamine or gabapentin or halazepam or haloperidol or hydroxyzine or imipramine or isocarboxazid or ketamine or ketazolam or ketotifen or labetalol or lamotrigine or levetiracetam or levomepromazine or lofepramine or lorazepam or meprobamate or methotrimeprazine or metoprolol or midazolam or milnacipran or mirtazapine or moclobemide or nadolol or nebivolol or nefazodone or nitrazepam or nortriptyline or olanzapine or ondansetron or oxazepam or oxprenolol or paroxetine or perphenazine or phenelzine or phenobarbital or phenytoin or pindolol or prazepam or pregabalin or primidone or promethazine or propofol or propranolol or quazepam or ramelteon or risperidone or sertraline or sotalol or temazepam or thioridazine or tiagabine or timolol or topiramate or tranlycypromine or trazodone or triazolam or trifluoperazine or trimipramine or tropisetron or valproate or venlafaxine or vigabatrin or zaleplon or zolpidem).mp.  
20 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19  
21 exp palliative therapy/  
22 exp terminally ill patient/  
23 exp terminal care/  
24 palliat\*.mp.  
25 (terminal\* adj6 (care or ill\* or disease\*)).mp.  
26 (terminal-stage\* or terminal stage\* or dying or (close adj6 death)).mp.  
27 (end adj3 life).mp.  
28 hospice\*.mp.  
29 ((end-stage\* or end stage\*) adj6 (disease\* or illness\* or care)).mp.  
30 (incurable adj6 (disease\* or illness\*)).mp.  
31 (advanced adj6 disease\*).mp.  
32 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31  
33 6 and 20 and 32  
34 crossover procedure/  
35 randomized controlled trial/  
36 single blind procedure/  
37 random\*.mp.  
38 factorial\*.mp.  
39 (crossover\* or cross over\* or cross-over).mp.  
40 placebo\*.mp.  
41 (doubl\* adj blind\*).mp.  
42 (singl\* adj blind\*).mp.  
43 assign\*.mp.  
44 allocat\*.mp.  
45 volunteer\*.mp.  
46 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45  
47 33 and 46  
key:  
[mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

## Appendix 5. PsycINFO search 2012

PsycINFO Ovid

1 exp anxiety/

2 exp anxiety disorders/

3 adjustment disorders/

4 Agitation/

5 restlessness/

6 (anxious\* or anxiet\* or agitat\* or restless\* or panic\* or stress\* or PTSD or phobia\* or phobic or nervous\* or obsessive compulsive disorder\* or OCD or adjustment disorder\*).mp.

7 1 or 2 or 3 or 4 or 5 or 6

8 exp drug therapy/

9 exp tranquilizing drugs/

10 exp antidepressant drugs/

11 benzodiazepines/

12 exp monoamine oxidase inhibitors/

13 exp neurotransmitter uptake inhibitors/

14 exp antihistaminic drugs/

15 exp barbiturates/

16 exp hypnotic drugs/

17 exp sedatives/

18 exp adrenergic blocking drugs/

19 (acebutolol or alimemazine or alprazolam or amitriptyline or atenolol or bisoprolol or bromazepam or bupropion or buspirone or carbamazepine or carisoprodol or carvedilol or celiprolol or clomipramine or chlorazepate or chlordiazepoxide or chlorphenamine or chlorpromazine or citalopram or clemastine or clobazam or clonazepam or co-tenidone or cyproheptadine or diazepam or desipramine or desvenlafaxine or dexmedetomidine or dosulepin or doxepin or droperidol or duloxetine or escitalopram or esmolol or estazolam or eszopiclone or etizolam or flunitrazepam or fluoxetine or flurazepam or fluvoxamine or gabapentin or halazepam or haloperidol or hydroxyzine or imipramine or isocarboxazid or ketamine or ketazolam or ketotifen or labetalol or lamotrigine or levetiracetam or levomepromazine or lofepramine or lorazepam or meprobamate or methotrimeprazine or metoprolol or midazolam or milnacipran or mirtazapine or moclobemide or nadolol or nebivolol or nefazodone or nitrazepam or nortriptyline or olanzapine or ondansetron or oxazepam or oxprenolol or paroxetine or perphenazine or phenelzine or phenobarbital or phenytoin or pindolol or prazepam or pregabalin or primidone or promethazine or propofol or propranolol or quazepam or ramelteon or risperidone or sertraline or sotalol or temazepam or thioridazine or tiagabine or timolol or topiramate or tranlycypromine or trazodone or triazolam or trifluoperazine or trimipramine or tropisetron or valproate or venlafaxine or vigabatrin or zaleplon or zolpidem).mp.

20 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19

21 palliative care/

22 hospice/

23 palliat\*.mp.

24 (terminal\* adj6 (care or ill\* or disease\*)).mp.

25 (terminal-stage\* or terminal stage\* or dying or (close adj6 death)).mp.

26 (end adj3 life).mp.

27 hospice\*.mp.

28 ((end-stage\* or end stage\*) adj6 (disease\* or illness\* or care)).mp.

29 (incurable adj6 (disease\* or illness\*)).mp.

30 (advanced adj6 disease\*).mp.

31 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

32 7 and 20 and 31

key:

mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures

## Appendix 6. CINAHL plus 2012

1. MW anxiety
2. MH exp adjustment disorders
3. MH agitation
4. (anxious\* or anxiet\* or agitat\* or restless\* or panic\* or stress\* or PTSD or phobia\* or phobic or nervous\* or obsessive compulsive disorder\* or OCD or adjustment disorder\*)
5. 1 or 2 or 3 or 4
6. MH exp drug therapy
7. MH exp tranquilizing agents
8. MH exp antidepressant agents
9. MH exp antianxiety agents
10. MH exp monoamine oxidase inhibitors
11. MH exp neurotransmitter uptake inhibitors
12. MH exp histamine agents
13. MH exp barbiturates
14. MH exp hypnotic and sedatives
15. MH exp adrenergic agents
16. MH exp antipsychotic agents
17. (acebutolol or alimemazine or alprazolam or amitriptyline or atenolol or bisoprolol or bromazepam or bupropion or buspirone or carbamazepine or carisoprodol or carvedilol or celiprolol or clomipramine or chlorazepate or chlordiazepoxide or chlorphenamine or chlorpromazine or citalopram or clemastine or clobazam or clonazepam or co-tenidone or cyproheptadine or diazepam or desipramine or desvenlafaxine or dexmedetomidine or dosulepin or doxepin or droperidol or duloxetine or escitalopram or esmolol or estazolam or eszopiclone or etizolam or flunitrazepam or fluoxetine or flurazepam or fluvoxamine or gabapentin or halazepam or haloperidol or hydroxyzine or imipramine or isocarboxazid or ketamine or ketazolam or ketotifen or labetalol or lamotrigine or levetiracetam or levomepromazine or lofepramine or lorazepam or meprobamate or methotrimeprazine or metoprolol or midazolam or milnacipran or mirtazapine or moclobemide or nadolol or nebivolol or nefazodone or nitrazepam or nortriptyline or olanzapine or ondansetron or oxazepam or oxprenolol or paroxetine or perphenazine or phenelzine or phenobarbital or phenytoin or pindolol or prazepam or pregabalin or primidone or promethazine or propofol or propranolol or quazepam or ramelteon or risperidone or sertraline or sotalol or temazepam or thioridazine or tiagabine or timolol or topiramate or tranlycypromine or trazodone or triazolam or trifluoperazine or trimipramine or tropisetron or valproate or venlafaxine or vigabatrin or zaleplon or zolpidem).mp.
18. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. MH palliative care
20. MH hospice
21. MH exp terminally ill patient
22. terminal care or ill\* or disease\*
23. terminal disease
24. terminal stage\* or terminal-stage\*
25. dying
26. hospice
27. end-stage or end stage
28. incurable disease
29. advanced disease
30. incurable illness
31. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32. 5 and 18 and 31

## Appendix 7. Antiepileptic drugs

To enhance the completeness of this review an additional search was run in January 2012 for antiepileptic drugs. The searches were run on MEDLINE, Embase, CINAHL, PsycINFO and CENTRAL. In these searches we used the following terms for the intervention: exp Antiepileptic Agents/

carbamazepine or eslicarbazepine or ethosuximide or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or phenobarbital or pregabalin or primidone or phenytoin or retigabine or rufinamide or tiagabine or topiramate or valproate or vigabatrin or zonisamide.

## Appendix 8. Searches run in May 2016

### CENTRAL (CRSO)

- #1 MESH DESCRIPTOR Anxiety EXPLODE ALL TREES 5582
- #2 MESH DESCRIPTOR Anxiety Disorders EXPLODE ALL TREES 4375
- #3 MESH DESCRIPTOR Adjustment Disorders EXPLODE ALL TREES 192
- #4 MESH DESCRIPTOR Psychomotor Agitation EXPLODE ALL TREES 602
- #5 ((anxious\* or anxiet\* or agitat\* or restless\* or panic\* or stress\* or PTSD or phobia\* or phobic or nervous\* or obsessive compulsive disorder\* or OCD or adjustment disorder\*)):TI,AB,KY 65130
- #6 #1 OR #2 OR #3 OR #4 OR #5 65442
- #7 MESH DESCRIPTOR drug therapy EXPLODE ALL TREES 117835
- #8 MESH DESCRIPTOR Anti-Anxiety Agents EXPLODE ALL TREES 8799
- #9 MESH DESCRIPTOR Antidepressive Agents EXPLODE ALL TREES 10354
- #10 MESH DESCRIPTOR Antipsychotic Agents EXPLODE ALL TREES 7126
- #11 MESH DESCRIPTOR Benzodiazepines EXPLODE ALL TREES 7745
- #12 MESH DESCRIPTOR Butyrophenones EXPLODE ALL TREES 1787
- #13 MESH DESCRIPTOR Phenothiazines EXPLODE ALL TREES 2181
- #14 MESH DESCRIPTOR Monoamine Oxidase Inhibitors EXPLODE ALL TREES 854
- #15 MESH DESCRIPTOR Serotonin Agents EXPLODE ALL TREES 11113
- #16 MESH DESCRIPTOR Histamine Agents EXPLODE ALL TREES 7708
- #17 MESH DESCRIPTOR Barbiturates EXPLODE ALL TREES 1837
- #18 MESH DESCRIPTOR Hypnotics and Sedatives EXPLODE ALL TREES 11260
- #19 MESH DESCRIPTOR Adrenergic Agents EXPLODE ALL TREES 27721
- #20 ((acebutolol or alimemazine or alprazolam or amitriptyline or atenolol or bisoprolol or bromazepam or bupropion or buspirone or carbamazepine or carisoprodol or carvedilol or celiprolol or clomipramine or chlorazepate or chlordiazepoxide or chlorphenamine or chlorpromazine or citalopram or clemastine or clobazam or clonazepam or co-tenidone or cyproheptadine or diazepam or desipramine or desvenlafaxine or dexmedetomidine or dosulepin or doxepin or duloxetine or escitalopram or esmolol or estazolam or eszopiclone or etizolam or flunitrazepam or fluoxetine or flurazepam or fluvoxamine or gabapentin or halazepam or haloperidol or hydroxyzine or imipramine or isocarboxazid or ketamine or ketazolam or ketotifen or labetalol or lamotrigine or levetiracetam or levomepromazine or lofepramine or lorazepam or meprobamate or methotrimeprazine or metoprolol or midazolam or milnacipran or mirtazapine or moclobemide or nadolol or nebivolol or nefazodone or nitrazepam or nortriptyline or olanzapine or ondansetron or oxazepam or oxprenolol or paroxetine or perphenazine or phenelzine or phenobarbital or phenytoin or pindolol or prazepam or pregabalin or primidone or promethazine or propranolol or quazepam or ramelteon or risperidone or sertraline or sotalol or temazepam or thioridazine or tiagabine or timolol or topiramate or tranlycypromine or trazodone or triazolam or trifluoperazine or trimipramine or tropisetron or valproate or venlafaxine or vigabatrin or zaleplon or zolpidem)):TI,AB,KY 59251
- #21 ((Lormetazepam or Loprazolam or Zopiclone or Chloral hydrate or Chlormethiazole or Clomethiazole or Pericyazine or Perphenazine or Prochlorperazine or Promazine or Paliperidone or Quetiapine or agomelatine or Reboxetine or Tryptophan or Acrivastine or Bilastine or Cetirizine or Desloratadine or Fexofenadine or Levocetirizine or loratadine or Mizolastine or Rupatadine or Trimeprazine)):TI,AB,KY 5824
- #22 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 190456
- #23 MESH DESCRIPTOR Palliative Care 1215
- #24 MESH DESCRIPTOR Terminal Care EXPLODE ALL TREES 315
- #25 MESH DESCRIPTOR Terminally Ill 60

#26 palliat\*:TI,AB,KY 3307  
 #27 ((terminal\* near6 (care or ill\* or disease\*)):TI,AB,KY 563  
 #28 ((terminal-stage\* or terminal stage\* or dying or (close adj6 death))):TI,AB,KY 510  
 #29 ((end adj3 life)):TI,AB,KY 352  
 #30 hospice\*:TI,AB,KY 280  
 #31 (((end-stage\* or end stage\*) adj6 (disease\* or illness\* or care))):TI,AB,KY 1869  
 #32 ((incurable adj6 (disease\* or illness\*)):TI,AB,KY 51  
 #33 ((advanced adj6 disease\*)):TI,AB,KY 2462  
 #34 #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 8421  
 #35 #6 AND #22 AND #34 90  
 #36 14/03/2012 TO 31/05/2016:DL 272867  
 #37 #35 AND #36 27

**MEDLINE (Ovid)**

1 exp Anxiety/ (64420)  
 2 exp Anxiety Disorders/ (69302)  
 3 Adjustment Disorders/ (4031)  
 4 Psychomotor Agitation/ (4308)  
 5 (anxious\* or anxiet\* or agit\* or restless\* or panic\* or stress\* or PTSD or phobia\* or phobic or nervous\* or obsessive compulsive disorder\* or OCD or adjustment disorder\*).mp. (1246199)  
 6 or/1-5 (1260505)  
 7 drug therapy.fs. (1854584)  
 8 exp Anti-Anxiety Agents/ (60302)  
 9 exp Antidepressive Agents/ (128780)  
 10 exp Antipsychotic Agents/ (110788)  
 11 exp Benzodiazepines/ (60534)  
 12 exp Butyrophenones/ (21427)  
 13 exp Phenothiazines/ (48388)  
 14 exp Monoamine Oxidase Inhibitors/ (20566)  
 15 exp Serotonin Agents/ (144506)  
 16 exp Histamine Agents/ (88729)  
 17 exp Barbiturates/ (52978)  
 18 exp "Hypnotics and Sedatives"/ (111515)  
 19 exp Adrenergic Agents/ (355644)  
 20 (acebutolol or alimemazine or alprazolam or amitriptyline or atenolol or bisoprolol or bromazepam or bupropion or buspirone or carbamazepine or carisoprodol or carvedilol or celiprolol or clomipramine or chlorazepate or chlordiazepoxide or chlorphenamine or chlorpromazine or citalopram or clemastine or clobazam or clonazepam or co-tenidone or cyproheptadine or diazepam or desipramine or desvenlafaxine or dexmedetomidine or dosulepin or doxepin or duloxetine or escitalopram or esmolol or estazolam or eszopiclone or etizolam or flunitrazepam or fluoxetine or flurazepam or fluvoxamine or gabapentin or halazepam or haloperidol or hydroxyzine or imipramine or isocarboxazid or ketamine or ketazolam or ketotifen or labetalol or lamotrigine or levetiracetam or levomepromazine or lofepramine or lorazepam or meprobamate or methotrimeprazine or metoprolol or midazolam or milnacipran or mirtazapine or moclobemide or nadolol or nebivolol or nefazodone or nitrazepam or nortriptyline or olanzapine or ondansetron or oxazepam or oxprenolol or paroxetine or perphenazine or phenelzine or phenobarbital or phenytoin or pindolol or prazepam or pregabalin or primidone or promethazine or propranolol or quazepam or ramelteon or risperidone or sertraline or sotalol or temazepam or thioridazine or tiagabine or timolol or topiramate or tranlycypromine or trazodone or triazolam or trifluoperazine or trimipramine or tropisetron or valproate or venlafaxine or vigabatrin or zaleplon or zolpidem).mp. (304943)  
 21 (Lormetazepam or Loprazolam or Zopiclone or Chloral hydrate or Chlormethiazole or Clomethiazole or Pericyazine or Perphenazine or Prochlorperazine or Promazine or Paliperidone or Quetiapine or agomelatine or Reboxetine or Tryptophan or Acrivastine or Bilastine or Cetirizine or Desloratadine or Fexofenadine or Levocetirizine or loratadine or Mizolastine or Rupatadine or Trimeprazine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (66773)  
 22 or/7-21 (2507015)  
 23 Palliative Care/ (44411)  
 24 exp Terminal Care/ (43801)

25 Terminally Ill/ (5769)  
 26 palliat\*.mp. (69308)  
 27 (terminal\* adj6 (care or ill\* or disease\*)).mp. (33751)  
 28 (terminal-stage\* or terminal stage\* or dying or (close adj6 death)).mp. (29543)  
 29 (end adj3 life).mp. (14084)  
 30 hospice\*.mp. (12120)  
 31 ((end-stage\* or end stage\*) adj6 (disease\* or illness\* or care)).mp. (33473)  
 32 (incurable adj6 (disease\* or illness\*)).mp. (2694)  
 33 (advanced adj6 disease\*).mp. (35405)  
 34 or/23-33 (202878)  
 35 randomized controlled trial.pt. (415460)  
 36 controlled clinical trial.pt. (90651)  
 37 randomized.ab. (312371)  
 38 placebo.ab. (158310)  
 39 drug therapy.fs. (1854584)  
 40 randomly.ab. (220598)  
 41 trial.ab. (323081)  
 42 groups.ab. (1391694)  
 43 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 (3523448)  
 44 exp animals/ not humans.sh. (4239199)  
 45 43 not 44 (3001538)  
 46 6 and 22 and 34 and 45 (1510)  
 47 (2012\* or 2013\* or 2014\* or 2015\* or 2016\*).ed. (3534743)  
 48 46 and 47 (382)

#### **Embase (Ovid)**

1 exp Anxiety/ (146866)  
 2 exp Anxiety Disorders/ (174195)  
 3 Adjustment Disorders/ (2312)  
 4 Psychomotor Agitation/ (5927)  
 5 (anxious\* or anxiet\* or agitat\* or restless\* or panic\* or stress\* or PTSD or phobia\* or phobic or nervous\* or obsessive compulsive disorder\* or OCD or adjustment disorder\*).mp. (2126678)  
 6 or/1-5 (2147293)  
 7 drug therapy.fs. (3275744)  
 8 exp Anti-Anxiety Agents/ (172725)  
 9 exp Antidepressive Agents/ (349098)  
 10 exp Antipsychotic Agents/ (244079)  
 11 exp Benzodiazepines/ (162297)  
 12 exp Butyrophenones/ (69061)  
 13 exp Phenothiazines/ (98054)  
 14 exp Monoamine Oxidase Inhibitors/ (44772)  
 15 exp Serotonin Agents/ (339905)  
 16 exp Histamine Agents/ (229873)  
 17 exp Barbiturates/ (139016)  
 18 exp "Hypnotics and Sedatives"/ (328978)  
 19 exp Adrenergic Agents/ (507749)  
 20 (acebutolol or alimemazine or alprazolam or amitriptyline or atenolol or bisoprolol or bromazepam or bupropion or buspirone or carbamazepine or carisoprodol or carvedilol or celiprolol or clomipramine or chlorazepate or chlordiazepoxide or chlorphenamine or chlorpromazine or citalopram or clemastine or clobazam or clonazepam or co-tenidone or cyproheptadine or diazepam or desipramine or desvenlafaxine or dexmedetomidine or dosulepin or doxepin or duloxetine or escitalopram or esmolol or estazolam or eszopiclone or etizolam or flunitrazepam or fluoxetine or flurazepam or fluvoxamine or gabapentin or halazepam or haloperidol or hydroxyzine or imipramine or isocarboxazid or ketamine or ketazolam or ketotifen or labetalol or lamotrigine or levetiracetam or levomepromazine or lofepramine or lorazepam or meprobamate or methotrimeprazine or metoprolol or midazolam or milnacipran or mirtazapine or moclobemide or nadolol or nebivolol or nefazodone or nitrazepam or nortriptyline or olanzapine or ondansetron or oxazepam or

oxprenolol or paroxetine or perphenazine or phenelzine or phenobarbital or phenytoin or pindolol or prazepam or pregabalin or primidone or promethazine or propranolol or quazepam or ramelteon or risperidone or sertraline or sotalol or temazepam or thioridazine or tiagabine or timolol or topiramate or tranlycypromine or trazodone or triazolam or trifluoperazine or trimipramine or tropisetron or valproate or venlafaxine or vigabatrin or zaleplon or zolpidem).mp. (712225)

21 (Lormetazepam or Loprazolam or Zopiclone or Chloral hydrate or Chlormethiazole or Clomethiazole or Pericyazine or Perphenazine or Prochlorperazine or Promazine or Paliperidone or Quetiapine or agomelatine or Reboxetine or Tryptophan or Acrivastine or Bilastine or Cetirizine or Desloratadine or Fexofenadine or Levocetirizine or loratadine or Mizolastine or Rupatadine or Trimeprazine).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (124603)

22 or/7-21 (4380654)

23 Palliative Care/ (48518)

24 exp Terminal Care/ (52379)

25 Terminally Ill/ (6594)

26 palliat\*.mp. (113733)

27 (terminal\* adj6 (care or ill\* or disease\*)).mp. (45785)

28 (terminal-stage\* or terminal stage\* or dying or (close adj6 death)).mp. (42652)

29 (end adj3 life).mp. (22725)

30 hospice\*.mp. (19005)

31 ((end-stage\* or end stage\*) adj6 (disease\* or illness\* or care)).mp. (58599)

32 (incurable adj6 (disease\* or illness\*)).mp. (4815)

33 (advanced adj6 disease\*).mp. (57862)

34 or/23-33 (315911)

35 random\$.tw. (1080929)

36 factorial\$.tw. (27596)

37 crossover\$.tw. (57278)

38 cross over\$.tw. (25537)

39 cross-over\$.tw. (25537)

40 placebo\$.tw. (237354)

41 (doubl\$ adj blind\$).tw. (167979)

42 (singl\$ adj blind\$).tw. (17556)

43 assign\$.tw. (285956)

44 allocat\$.tw. (103682)

45 volunteer\$.tw. (206547)

46 Crossover Procedure/ (46987)

47 double-blind procedure.tw. (235)

48 Randomized Controlled Trial/ (403142)

49 Single Blind Procedure/ (22048)

50 or/35-49 (1693538)

51 (animal/ or nonhuman/) not human/ (5029808)

52 50 not 51 (1503726)

53 6 and 22 and 34 and 52 (591)

54 (2012\* or 2013\* or 2014\* or 2015\* or 2016\*).dd. (6852351)

55 53 and 54 (227)

#### **PsycINFO (Ovid)**

1 exp Anxiety/ (58004)

2 exp Anxiety Disorders/ (68090)

3 Adjustment Disorders/ (570)

4 Agitation/ (1198)

5 restlessness/ (321)

6 (anxious\* or anxiet\* or agitat\* or restless\* or panic\* or stress\* or PTSD or phobia\* or phobic or nervous\* or obsessive compulsive disorder\* or OCD or adjustment disorder\*).mp. (486813)

7 or/1-6 (487305)

8 exp drug therapy/ (125834)

- 9 exp tranquilizing drugs/ (41641)
- 10 exp antidepressant drugs/ (34233)
- 11 benzodiazepines/ (4635)
- 12 exp monoamine oxidase inhibitors/ (2163)
- 13 exp neurotransmitter uptake inhibitors/ (12703)
- 14 exp antihistaminic drugs/ (984)
- 15 exp barbiturates/ (2092)
- 16 exp hypnotic drugs/ (5517)
- 17 exp sedatives/ (18535)
- 18 exp adrenergic blocking drugs/ (3619)
- 19 (acebutolol or alimemazine or alprazolam or amitriptyline or atenolol or bisoprolol or bromazepam or bupropion or buspirone or carbamazepine or carisoprodol or carvedilol or celiprolol or clomipramine or chlorazepate or chlordiazepoxide or chlorphenamine or chlorpromazine or citalopram or clemastine or clobazam or clonazepam or co-tenidone or cyproheptadine or diazepam or desipramine or desvenlafaxine or dexmedetomidine or dosulepin or doxepin or duloxetine or escitalopram or esmolol or estazolam or eszopiclone or etizolam or flunitrazepam or fluoxetine or flurazepam or fluvoxamine or gabapentin or halazepam or haloperidol or hydroxyzine or imipramine or isocarboxazid or ketamine or ketazolam or ketotifen or labetalol or lamotrigine or levetiracetam or levomepromazine or lofepramine or lorazepam or meprobamate or methotrimeprazine or metoprolol or midazolam or milnacipran or mirtazapine or moclobemide or nadolol or nebivolol or nefazodone or nitrazepam or nortriptyline or olanzapine or ondansetron or oxazepam or oxprenolol or paroxetine or perphenazine or phenelzine or phenobarbital or phenytoin or pindolol or prazepam or pregabalin or primidone or promethazine or propranolol or quazepam or ramelteon or risperidone or sertraline or sotalol or temazepam or thioridazine or tiagabine or timolol or topiramate or transylpromine or trazodone or triazolam or trifluoperazine or trimipramine or tropisetron or valproate or venlafaxine or vigabatrin or zaleplon or zolpidem).mp. (66204)
- 20 (Lormetazepam or Loprazolam or Zopiclone or Chloral hydrate or Chlormethiazole or Clomethiazole or Pericyazine or Perphenazine or Prochlorperazine or Promazine or Paliperidone or Quetiapine or agomelatine or Reboxetine or Tryptophan or Acrivastine or Bilastine or Cetirizine or Desloratadine or Fexofenadine or Levocetirizine or loratadine or Mizolastine or Rupatadine or Trimeprazine).mp. (8915)
- 21 or/8-20 (180411)
- 22 palliative care/ (8996)
- 23 hospice/ (2649)
- 24 palliat\*.mp. (11674)
- 25 (terminal\* adj6 (care or ill\* or disease\*)).mp. (6641)
- 26 (terminal-stage\* or terminal stage\* or dying or (close adj6 death)).mp. (31725)
- 27 (end adj3 life).mp. (7716)
- 28 hospice\*.mp. (4266)
- 29 ((end-stage\* or end stage\*) adj6 (disease\* or illness\* or care)).mp. (1314)
- 30 (incurable adj6 (disease\* or illness\*)).mp. (402)
- 31 (advanced adj6 disease\*).mp. (2076)
- 32 or/22-31 (48760)
- 33 7 and 21 and 32 (404)
- 34 clinical trials/ (9558)
- 35 (randomis\* or randomiz\*).tw. (60920)
- 36 (random\$ adj3 (allocat\$ or assign\$)).tw. (34606)
- 37 ((clinic\$ or control\$) adj trial\$).tw. (51502)
- 38 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw. (22211)
- 39 (crossover\$ or "cross over\$").tw. (8245)
- 40 random sampling/ (688)
- 41 Experiment Controls/ (855)
- 42 Placebo/ (4532)
- 43 placebo\$.tw. (34693)
- 44 exp program evaluation/ (17993)
- 45 treatment effectiveness evaluation/ (19892)
- 46 ((effectiveness or evaluat\$) adj3 (stud\$ or research\$)).tw. (69778)
- 47 or/34-46 (218371)

48 33 and 47 (67)

49 limit 48 to yr="2012 -Current" (25)

**CINAHL (EBSCO)**

S47 S45 AND S46

S46 EM 20120101-20160531

S45 S35 AND S44

S44 S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43

S43(allocat\* random\*)

S42(MH "Quantitative Studies")

S41 (MH "Placebos")

S40 placebo\*

S39(random\* allocat\*)

S38 (MH "Random Assignment")

S37 (Randomi?ed control\* trial\*)

Search modes - Boolean/Phrase

S36 (singl\* blind\* ) or (doubl\* blind\* ) or (tripl\* blind\* ) or (trebl\* blind\* ) or (trebl\* mask\* ) or (tripl\* mask\* ) or (doubl\* mask\* ) or (singl\* mask\* )

S35 S6 AND S22 AND S34

S24 S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33

S33 (advanced N6 disease\*)

S32 (incurable N6 (disease\* or illness\*))

S31 ((end-stage\* or end stage\*) N6 (disease\* or illness\* or care))

S30 hospice\*

S29 (end N3 life)

S28 (terminal-stage\* or terminal stage\* or dying or (close N6 death))

S27 (terminal\* N6 (care or ill\* or diseas\*))

S26 palliat\*

S25 (MH "Terminally Ill Patients")

S24 (MH "Terminal Care+")

S23 (MH "Palliative Care")

S22 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21

S21 (Lormetazepam or Loprazolam or Zopiclone or Chloral hydrate or Chlormethiazole or Clomethiazole or Pericyazine or Perphenazine or Prochlorperazine or Promazine or Paliperidone or Quetiapine or agomelatine or Reboxetine or Tryptophan or Acrivastine or Bilastine or Cetirizine or Desloratadine or Fexofenadine or Levocetirizine or loratadine or Mizolastine or Rupatadine or Trimeprazine)

S20(acebutolol or alimemazine or alprazolam or amitriptyline or atenolol or bisoprolol or bromazepam or bupropion or buspirone or carbamazepine or carisoprodol or carvedilol or celiprolol or clomipramine or chlorazepate or chlordiazepoxide or chlorphenamine or chlorpromazine or citalopram or clemastine or clobazam or clonazepam or co-tenidone or cyproheptadine or diazepam or desipramine or desvenlafaxine or dexmedetomidine or dosulepin or doxepin or duloxetine or escitalopram or esmolol or estazolam or eszopiclone or etizolam or flunitrazepam or fluoxetine or flurazepam or fluvoxamine or gabapentin or halazepam or haloperidol or hydroxyzine or imipramine or isocarboxazid or ketamine or ketazolam or ketotifen or labetalol or lamotrigine or levetiracetam or levomepromazine or lofepramine or lorazepam or meprobamate or methotrimeprazine or metoprolol or midazolam or milnacipran or mirtazapine or moclobemide or nadolol or nebivolol or nefazodone or nitrazepam or nortriptyline or olanzapine or ondansetron or oxazepam or oxprenolol or paroxetine or perphenazine or phenelzine or phenobarbital or phenytoin or pindolol or prazepam or pregabalin or primidone or promethazine or propranolol or quazepam or ramelteon or risperidone or sertraline or sotalol or temazepam or thioridazine or tiagabine or timolol or topiramate or tranlycypromine or trazodone or triazolam or trifluoperazine or trimipramine or tropisetron or valproate or venlafaxine or vigabatrin or zaleplon or zolpidem)

S19 (MH "Adrenergic Agents+")

S18 (MH "Hypnotics and Sedatives+")

S17 (MH "Barbiturates+")

S16 (MH "Histamine Agents+")

S15 (MH "Serotonin Agents+")

S14 (MH "Monoamine Oxidase Inhibitors+")

S13 (MH "Antipsychotic Agents, Phenothiazine+")

S12 (MH "Antipsychotic Agents, Butyrophenone+")  
 S11 (MH "Antianxiety Agents, Benzodiazepine+")  
 S10 (MH "Antipsychotic Agents+")  
 S9 (MH "Antidepressive Agents+")  
 S8 (MH "Antianxiety Agents+")  
 S7 (MH "Drug Therapy+")  
 S6 S1 OR S2 OR S3 OR S4 OR S5  
 S5 (anxious\* or anxiet\* or agitat\* or restless\* or panic\* or stress\* or PTSD or phobia\* or phobic or nervous\* or obsessive compulsive disorder\* or OCD or adjustment disorder\*)  
 S4 (MH "Psychomotor Agitation")  
 S3 (MH "Adjustment Disorders")  
 S2 (MH "Anxiety Disorders+")  
 S1 (MH "Anxiety+")

## Appendix 9. Searches run in May 2016 for additional drugs

### MEDLINE (Ovid)

1 exp Anxiety/ (64499)  
 2 exp Anxiety Disorders/ (69373)  
 3 Adjustment Disorders/ (4031)  
 4 Psychomotor Agitation/ (4313)  
 5 (anxious\* or anxiet\* or agitat\* or restless\* or panic\* or stress\* or PTSD or phobia\* or phobic or nervous\* or obsessive compulsive disorder\* or OCD or adjustment disorder\*).mp. (1247558)  
 6 or/1-5 (1261866)  
 7 (Lormetazepam or Loprazolam or Zopiclone or Chloral hydrate or Chlormethiazole or Clomethiazole or Pericyazine or Perphenazine or Prochlorperazine or Promazine or Paliperidone or Quetiapine or agomelatine or Reboxetine or Tryptophan or Acrivastine or Bilastine or Cetirizine or Desloratadine or Fexofenadine or Levocetirizine or loratadine or Mizolastine or Rupatadine or Trimeprazine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (66822)  
 8 Palliative Care/ (44450)  
 9 exp Terminal Care/ (43827)  
 10 Terminally Ill/ (5772)  
 11 palliat\*.mp. (69375)  
 12 (terminal\* adj6 (care or ill\* or disease\*)).mp. (33771)  
 13 (terminal-stage\* or terminal stage\* or dying or (close adj6 death)).mp. (29569)  
 14 (end adj3 life).mp. (14104)  
 15 hospice\*.mp. (12129)  
 16 ((end-stage\* or end stage\*) adj6 (disease\* or illness\* or care)).mp. (33508)  
 17 (incurable adj6 (disease\* or illness\*)).mp. (2698)  
 18 (advanced adj6 disease\*).mp. (35450)  
 19 or/8-18 (203067)  
 20 randomized controlled trial.pt. (415956)  
 21 controlled clinical trial.pt. (90682)  
 22 randomized.ab. (312879)  
 23 placebo.ab. (158504)  
 24 drug therapy.fs. (1856488)  
 25 randomly.ab. (220900)  
 26 trial.ab. (323631)  
 27 groups.ab. (1393402)  
 28 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (3527435)  
 29 exp animals/ not humans.sh. (4241825)  
 30 28 not 29 (3005030)

**WHAT'S NEW**

Last assessed as up-to-date: 17 May 2016.

Date	Event	Description
28 February 2017	New citation required but conclusions have not changed	The list of drugs to search for was updated and a database search for these rerun for all years up to May 2016. From the searches, no new studies to include were identified. We updated the background sections with more recent references. We listed primary and secondary outcomes of interest. We planned to construct a 'Summary of findings' table and assess the quality of the evidence using the GRADE approach. The authorship was changed
15 December 2016	New search has been performed	This review was updated to include the results of a new search on 17 May 2016

**HISTORY**

Protocol first published: Issue 1, 2004

Review first published: Issue 1, 2004

Date	Event	Description
29 February 2012	New citation required but conclusions have not changed	A search for new studies was conducted to January 2012 and no new included studies were identified. Two new studies were excluded (Koralewski 2002; Ziolkko 2004). As part of the update the Background, Methods and Discussion were updated and the authorship changed
29 February 2012	New search has been performed	This review is an update of the original review published in Issue 1, 2004 of the Cochrane Library
27 October 2008	Amended	Converted to new review format.

## CONTRIBUTIONS OF AUTHORS

2012 update:

- all authors revised the search strategy;
- LJ and BC screened studies;
- KCJ, AT, MK and LJ commented on the draft review;
- all authors agreed the final document.

2017 update:

- SS updated the drugs listed in the search strategy;
- SS and CM searched trials registers and handsearched conference abstracts;
- SS and CM undertook screening of papers with deferment to NP for points of disagreement;
- all authors commented on the draft manuscript and agreed the final version.

## DECLARATIONS OF INTEREST

SS: none known; SS is a specialist in palliative care and manages patients with anxiety.

CM: none known.

NP: none known.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

**2012 update**

- The Background, Methods, Results and Discussion were updated and revised to conform with current Cochrane style guidelines.

**2017 update**

- In the first update and this second update we searched a range of trial registers that were not searched in the original Cochrane Review. However, while the ISRCTN Trials Register ([www.controlled-trials.com/isrctn](http://www.controlled-trials.com/isrctn)) was searched in the first update, it was not searched in this latest update as it is covered by WHO Portal.
  - We did not search the Cochrane Pain, Palliative & Supportive Care Register as its contents are captured by CENTRAL.
  - We added an additional 25 drugs to our search and thus database searches for these were rerun from 2012 (see [Appendix 9](#)).
  - We updated the Background section to include references to more recently published work.
  - We updated the Methods section to take into account changes in the search strategy. We thought that we should be searching for studies currently in progress, in addition to published studies, and thus undertook searches of trial registers.
    - We added new outcomes, and specified primary and secondary outcomes. We specified that we will report outcomes assessed at one week.
    - We changed the description of 'Types of participants' and 'Types of interventions' to reflect current terminology. We also added comparators of interest.
      - We expanded our risk of bias descriptions.
      - We stated that we planned to construct a 'Summary of findings' table and to assess the quality of the evidence used the GRADE approach.
    - The Results and Discussion sections were updated to take into account the fact that no studies were found to include in the review and to include references to more recently published work.
    - All sections were updated and revised to conform with current Cochrane style guidelines.

## **INDEX TERMS**

### **Medical Subject Headings (MeSH)**

\*Palliative Care; Anti-Anxiety Agents [\*therapeutic use]; Anxiety [\*drug therapy]; Terminally Ill [\*psychology]

### **MeSH check words**

Adult; Humans