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Benzodiazepines for anxiety

Summary of systematic reviews

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CONTENTS

Benzodiazepines for anxiety

Plain language summary

Anxiety disorders are the most common mental disorders. About one in four adults in Australia has an anxiety disorder at some time in their life. This can be associated with severe distress. It can lead to disrupted social life and poor health.

Benzodiazepines are used by doctors to treat anxiety.

Based on 118 studies, it is unclear if benzodiazepines help to treat anxiety. Some studies found benzodiazepines help, while others did not. They were not good quality studies.

All agreed that there are possible harms with benzodiazepines. They say that doctors must carefully judge the risks and benefits before prescribing them.

BACKGROUND & METHODS

Benzodiazepines have been widely used in clinical practice since their introduction in the 1950's and continue to be one of the most consumed and highly prescribed class of drugs. Their range of action (sedative/hypnotic, anxiolytic, anticonvulsant and muscle relaxant), combined with their low toxicity and cost has gained them popularity among physicians and patients.[1] Since the early 1980's, studies have regularly pointed out the risks related to long term use of benzodiazepines. These include physical dependence, withdrawal symptoms and other adverse effects such as cognitive impairments and an increased risk of falls and fractures, particularly in elderly patients.[2]

The TAC and WorkSafe Victoria requested an evidence review on the use of hypnosedatives (licensed for use in Australia) for anxiety, insomnia and muscle spasm. To identify the scope of the research, an evidence map was developed as a first step to determine the quantity and complexity of systematic reviews (SR) and evidence-based guidelines (EBG) on the topic.[3] The evidence map identified 34 SRs and seven EBGs on hypnosedatives for anxiety, insomnia or muscle spasm (see Table A2.2). A summary of the evidence map and a detailed description of the evidence map methodology can be found in Appendices 2 and 3, respectively.

Given the breadth of the evidence indentified, the topic was refined to a review of SRs on benzodiazepines for anxiety disorders related to traffic accidents or workplace injuries. The details of these SRs were summarized and their methodological quality assessed using a measurement tool for *assessment of multiple systematic reviews* (AMSTAR).[4] The AMSTAR is an eleven item tool designed to give an overall quality score for SRs. These scores give an indication of the risk of bias of each SR with 0/11 representing lowest quality (highest risk of bias), and 11/11 highest quality (lowest risk of bias).

In this report we present a summary of the existing systematic reviews on the effectiveness of benzodiazepines for anxiety disorders. This is intended to provide an overview of the large and complicated body of evidence underlying these commonly prescribed drugs.

FINDINGS

A total of ten systematic reviews of the effectiveness of benzodiazepines for anxiety disorders were identified. Five reviews investigated the use of benzodiazepines for generalized anxiety disorder (Table 1), two reviews assessed their use for panic disorder (Table 2) and three reviews focused on other types of anxiety (Table 3).

The number of benzodiazepines investigated by each SR ranged from 1 to 5. Alprazolam was the most investigated drug appearing in all of the 10 SRs, followed by Diazepam (n=8) and Lorazepam (n=6). Overall, the quality of the included systematic reviews was low, with six studies having a quality score of 5/11 or less (see Table 4). Three reviews achieved an AMSTAR score higher than 7/11. Table 4 presents the methodological quality of each included SR with regard to the different AMSTAR rating items. Characteristics and results of the included SRs are presented in Tables 1-3, and in greater detail in Appendix 1.

Generalized Anxiety disorder

Five SRs conducted between 1997 and 2007[5-9] investigated the effect of benzodiazepines on GAD. These reviews all addressed slightly different research questions in regard to drugs studied, duration of treatment, comparators, and outcomes measured (see Table 1).

The drugs and comparators studied across the five SRs differed as follows. Only one review[8] focused exclusively on benzodiazepines and included RCTs that compared diazepam, lorazepam or alprazolam against placebo. One review[9] compared the effectiveness of benzodiazepines and azapirones against placebo. Two reviews[5, 6] examined the effectiveness of benzodiazepines and several other classes of drugs compared to placebo, and one SR[7] included placebo-controlled trials as well as trials comparing effectiveness between drugs. The review by Gould[5] also looked at the effectiveness of psychological treatments for GAD.

There were also differences in the outcomes reported in each SR. Three of the reviews[5, 6, 9] reported the effectiveness of benzodiazepines as pooled effect sizes based on behavioural tests of anxiety scores. While, one review[8] measured effectiveness as the risk ratio of withdrawing from benzodiazepine-based treatments compared to placebo.

In terms of duration of treatment, the study by Mahe et al.[7] was the only SR to investigate the long-term effect of benzodiazepines on GAD by including studies of more than 8 weeks duration. Two SRs [8, 9] drew conclusions on the short-term effects of benzodiazepines, with most of the included studies in Martin et al.[8] lasting 4-weeks or less, and an average duration of treatment of 5.3 weeks for the studies included in Mitte et al.[9]. The remaining two SRs, Gould et al.[5] and Hidalgo et al.[6], included trials of various durations ranging between 2 to 9 weeks, and 4 to 12 weeks, respectively.

We identified important differences in methodological quality between the five included SRs (see Table 4). Among these reviews, Mitte et al.[9] presented the lowest risk of bias with an AMSTAR score of 8/11 (see Table 1). This SR included 26 relevant studies (mostly on diazepam, alprazolam and lorazepam vs. pill placebo). The review compared azapirones, benzodiazepines and placebo, and

found that both benzodiazepines and azapirones were more effective than placebo in reducing anxiety and comorbid depression in GAD. Although no difference in efficacy was found between drug classes, patient compliance was better with benzodiazepine-based treatment compared to other pharmacological approaches. Based on this result, the review suggests that benzodiazepines are to be preferred to other drugs as a short term treatment strategy. The authors suggest limiting prescriptions to short-term use due to the increasing risk of serious adverse effects following long-term use such as physical dependence, withdrawal, and memory loss. They also highlight several methodological limitations in the included studies such as the lack of double-blindness, which can result in an overly positive outcome and a biased estimation of efficacy. Another issue in most of these studies concerns the lack of assessment of how the treatment impacts on patients' quality of life.

Panic disorder

Two SRs investigated the effect of benzodiazepines on panic disorder[10, 11] (see Table 2). The review by Cox et al.[10] assessed the efficacy of alprazolam, imipramine and exposure to phobic situations as treatments for panic disorder with agoraphobia (PDA). The review suggests that alprazolam and exposure therapies are both effective for PDA. However, the study has numerous methodological flaws; for example, no details of the included studies are provided meaning that it is not possible to determine the quality of the research upon which the findings are based. Overall the SR by Cox et al.[10] has a high risk of bias (AMSTAR score of 2/11), which limits the validity of its conclusions.

The SR by Watanabe et al.[11] compared the effectiveness of different treatment strategies combining benzodiazepines and psychotherapy and presented the lowest risk of bias with an AMSTAR score of 10/11. The review included three trials involving 166 participants and provided data on 2 different benzodiazepines. No statistically significant difference was found between the different strategies assessed (combination of psychotherapy and benzodiazepines vs. psychotherapy alone). The main conclusion from the review was that there is inadequate evidence to assess the effectiveness of psychotherapy combined with benzodiazepines for panic disorder. This was due to a lack of high-quality trials; three RCTs were identified, only two of which could contribute data to the primary outcomes of the review (see Table 2).

Other types of anxiety

Three SRs assessed the effectiveness of benzodiazepines for other types of anxiety[12-14] (see Table 3). The review by Wetherell et al.[14] investigated all treatments of geriatric anxiety disorders. Among the pharmacological interventions identified, the review found three RCTs investigating the impact of benzodiazepines for anxiety disorders in later life, only one of these was relevant to this report. This RCT was stopped prematurely due to concerns about adverse events and high attrition, resulting in sample sizes that were too small to generate solid conclusions about efficacy. Overall, the authors of the SR noted the value of short-term use of benzodiazepines, and the potential adverse effects associated with long-term use.

Inada et al.[13] conducted a systematic review of Japanese trials investigating the effectiveness of diazepam in improving anxiety states in patients with neurosis or psychosomatic disease. The review

included 17 placebo-controlled RCTs conducted between 1970 and 1992. The study found diazepam to be significantly more effective than placebo with an optimal treatment regimen of 12 or 18mg/day dose over a period of two weeks or more. The authors stated that the quality of the 17 RCTs selected was high. However, they also noted that an intention to treat analysis of the data was performed in only seven studies and that several studies reported a large number of dropouts. These methodological shortcomings were not accounted for in the meta-analysis and represent an important source of bias for the pooled estimates reported in the SR. This SR had high risk of bias (AMSTAR score of 3/11), therefore, the findings and conclusions of this review should be interpreted with caution.

The review by Furukawa et al.[12] had the highest methodological quality with an AMSTAR score of 9/11. It investigated the effects of combining benzodiazepines with antidepressants for the treatment of adults with anxiety associated with major depression. The review included 10 randomized controlled trials (RCTs) and meta-analysed the results of 731 patients. The included RCTs varied in terms of quality, with two considered high quality, four intermediate quality and two low quality (due to uncertainties about blinding, or high drop-out rates). The authors noted that only one trial followed patients beyond eight weeks, and that some of the included studies had conflicting findings, making them hard to interpret and generalise. Overall, the review found that combining benzodiazepines with antidepressants was superior to treatment with antidepressants alone in terms of depressive symptoms and anxiety severity. The authors also emphasized the risk of dependence and withdrawal syndrome associated with the use of benzodiazepines and recommended that clinicians carefully assess the benefits and risks before prescribing this class of drug to a patient.

SUMMARY

Overall, there is a lack of consistency across the SRs' findings and a high risk of bias (low AMSTAR scores) for most studies. Each SR aimed to answer a slightly different question (i.e. different populations, drugs, comparators, or outcomes studied) making their results difficult to combine into an overall answer on the effectiveness of benzodiazepines as a treatment for anxiety.

The five SRs assessing the effect of benzodiazepines on GAD included a total of 41 different trials investigating six out of the eleven types of benzodiazepines registered in Australia. Three multifaceted reviews,[5, 6, 9] including the one with the highest AMSTAR score (8/11), concluded that benzodiazepines were an effective short-term treatment for patients with GAD. Another review found that the available evidence was inconclusive.[7] The only SR that exclusively focused on benzodiazepines was unable to find convincing evidence of their effectiveness. Using an outcome measure based on patients' withdrawal rates, the review by Martin et al.[8] showed that subjects receiving benzodiazepines withdrew from treatment at the same rate as those receiving placebo pills. It is important to note that none of these reviews compared effects benzodiazepines with psychological treatments, which do not carry a risk of physical dependence.

For panic disorder, a high-quality Cochrane SR[11] assessing the effectiveness of benzodiazepines combined with psychotherapy was unable to draw conclusions due to the poor quality of the available evidence.

The same uncertainty exists among the reviews addressing the effects of benzodiazepines for other types of anxiety. For example, the evidence of effectiveness reported by Inada et al.[13] is limited by the important methodological shortcomings of the RCTs included in the review. The SR by Furukawa et al.[12] does not allow us to draw any conclusion on the specific effect benzodiazepines as the review reports the results of a combination of benzodiazepines and antidepressants, rather than the effects of benzodiazepines alone.

The major methodological differences existing between the included SRs prevent an overall interpretation of their findings. Further, all positive results should be interpreted with caution due to the methodological shortcomings of the included RCTs, and the potential publication bias (i.e. non-publication of non-statistically significant results) inherent to all SRs and meta-analyses. Another important point which has been consistently discussed in all the included SRs concerns the potential adverse effects related to the use of benzodiazepines and the necessity to carefully assess benefits and possible harms before prescribing them.

SUMMARY TABLES

Table 1. Systematic reviews of benzodiazepines for Generalised Anxiety Disorder

STUDY	Gould 1997(5)	Hidalgo 2007(6)	Mahe 2000(7)	Martin 2007(8)	Mitte 2005(9)
AMSTAR RATING	4/11	5/11	2/11	6/11	8/11
BENZODIAZEPINES*					
Alprazolam	3 studies	1 study	1 study	4 studies	6 studies
Bromazepam	3 studies				3 studies
Clobazam	1 study		1 study		
Diazepam	8 studies	1 study	7 studies	12 studies	13 studies
Flunitrazepam					
Lorazepam	5 studies	2 studies	3 studies	7 studies	7 studies
Midazolam					
Nitrazepam					
Oxazepam					
Temazepam					
Triazolam					1 study
COMPARATORS OF INTEREST	**Pharmacotherapy vs Placebo** Total included drug studies (n=22) **Relevant studies (n= 17)** Irrelevant studies (n=5)	**Pharmacotherapy vs Placebo** Total included studies (n=21) **Relevant studies (n= 4)** Irrelevant studies (n=22)	**Pharmacotherapy vs placebo or other drugs** Total included studies (n=13) **Relevant studies (n=8)** Irrelevant studies (n=5)	**Benzodiazepine vs placebo** Total included studies (n=23) **Relevant studies (n= 23)** Irrelevant studies (n=0)	**Pharmacotherapy vs placebo** Total included studies (n=48) **Relevant studies (n=26)** Irrelevant studies (n=22)
DURATION OF TREATMENT	Not specified	Not specified	Long-term (8 weeks or longer)	**Short-term (not defined)**	Short-term (not defined)
OUTCOMES	Measure of anxiety or worry & measure of depression (effect size)	Measure of anxiety (effect size)	Benefits to patients/ successful long-term treatment of anxiety Measure of anxiety	**Efficacy:** as measured by withdrawals from study **Side effects:** as measured by withdrawals due to adverse events	Anxiety, depression, quality of life, or clinical significance (only pertaining to anxiety).
RESULTS AND CONCLUSIONS	**EFFECTIVE** **(more effective than placebo)** Benzos in order of effectiveness from most to least: Diazepam, Lorazepam, Bromazepam, Alprazolam	**EFFECTIVE (low to moderate)** Order of effectiveness from most to least: Pregabalin, Hydroxyzine, Venlafaxine SR, Benzos, SSRIs, Buspirone, complementary and alternative medicines.	**INCONCLUSIVE** Evidence of effectiveness is inconclusive	**NOT EFFECTIVE** **(not more effective than placebo)** Benzos are not effective for the short-term treatment of GAD (no difference between benzos and placebo)	**EFFECTIVE** **(more effective than placebo)** Benzos and azapirones equally effective, both classes of drug more effective than placebo for short-term treatment
COMMENTS	this review also looked at psychological treatments vs control (n=13)	A study of bromazepam was included in the review, but efficacy data was not reported and not included in the analysis"	This review looks at long-term treatment of GAD (8 weeks or longer) n.b. this review also looked at treatment for non well-defined anxiety disorder (n=5 studies)		This review looked at benzos vs placebo,and azapirones vs placebo and then compared effect sizes

**for some SRs the numbers of studies for each benzodiazepine do not add up to the total number of relevant studies, as some trials studied more than one type of benzodiazepine.*

KEY: GAD = Generalised Anxiety Disorder Benzo/s = Benzodiazepine/s SSRIs = Selective Serotonin Reuptake Inhibitors

Table 2. Systematic reviews of benzodiazepines for Panic Disorder

STUDY	Cox 1992(10)	Watanabe 2009(11)
AMSTAR RATING	2/11	10/11
BENZODIAZPINES*		
Alprazolam	✓**	2 studies
Bromazepam		
Clobazam		
Diazepam		1 study
Flunitrazepam		
Lorazepam		
Midazolam		
Nitrazepam		
Oxazepam		
Temazepam		
Triazolam		
COMPARATORS OF INTEREST	This meta-analysis calculated and compared effect sizes of alprazolam, Imipramine and exposure therapy Included studies (n=34) **No list or details of included studies were provided, therefore, it was not possible to list the included studies determine the number of studies of alprazolam or determine the comparators used in these	**benzos + psychotherapy vs (psychotherapy alone or benzo treatment)** Total included studies (n=3) **Total relevant studies (n=3)** Irrelevant studies (n=0)
OUTCOMES	1/ Dysphoria or depression 2/ Frequency of panic attacks per week 3/ Severity of panic attacks 4/ Agoraphobic fear 5/ Agoraphobic avoidance behaviour 6/ Generalized anxiety 7/ Overall improvement ratings	***Primary outcome(s):*** "Response" (as defined by authors of included studies), or a Panic Disorder Severity Scale (PDSS) score of 7 or below. ***Secondary outcome(s):*** 1. Panic disorder global severity on a continuous scale 2. Frequency or severity of panic attacks 3. Phobic avoidance 4. General anxiety 5. Depression 6. Social functioning 7. Quality of life 8. Patient satisfaction with treatment 9. Economic costs
CONCLUSIONS	**EFFECTIVE** Alprazolam and exposure therapies both effective for PDA Alprazolam was significantly effective for panic and anxiety variables in PDA, while exposure was significantly effective for phobia variables. Exposure had the most consistently strong effect sizes Alprazolam was not effective for agoraphobic dimensions	**INSUFFICIENT EVIDENCE** Insufficient evidence to assess clinical effects of benzodiazepines + psychotherapy for panic disorder

**for some SRs the numbers of studies for each benzodiazepine do not add up to the total number of relevant studies, as some trials studied more than one type of benzodiazepine.*

KEY: PDA = Panic Disorder with Agoraphobia Benzo/s = Benzodiazepine/s

Table 3. Systematic reviews of benzodiazepines for other types of anxiety

STUDY	Furukawa 2001(12)	Inada 2003(13)	Wethrell 2005(14)
AMSTAR RATING	9/11	3/11	5/11
TYPE OF ANXIETY	anxiety associated with major depression	neurosis or psychosomatic disease	any anxiety disorder
BENZODIAZEPINES*			
Alprazolam	1 study	1 study	1 study
Bromazepam			
Clobazam		2 studies	
Diazepam	1 study	17 studies	
Flunitrazepam	1 study		
Lorazepam		1 study	
Midazolam			
Nitrazepam			
Oxazepam			
Temazepam			
Triazolam	1 study		
COMPARATORS OF INTEREST	Antidepressant + benzo vs antidepressant alone Total Included studies (n=10) Relevant included studies (n= 4)	both diazepam and placebo were used as controls on all studies Total Included studies (n=17) Relevant included studies (n= 17)	Benzo vs antidepressant vs placebo Total included pharmalogical studies (n=8) Relevant included studies (n=1)
OUTCOMES	**Primary outcome**: Depressive severity, (at least one measure) Symptom severity (self-report or observer-rating) **Secondary outcomes**: 1. Response in depression; 2. Acceptability of treatment; 3. Anxiety severity; 4. Insomnia severity; 5. Side effects	Final Global Improvement Rating scale (FGIR) used to capture "changes in the overall severity of patient symptoms" expressed as a Relative Risk after meta-analysis	effect size for each outcome measure (including: CGI, Clinical Global Impression; HAMA, Hamilton Anxiety Scale; STAI, Spielberger State-Trait Anxiety Inventory; VAS, Visual Analogue Scale)
CONCLUSIONS	**EFFECTIVE, BUT BENEFITS SHOULD BE WEIGHED AGAINST RISKS**	**EFFECTIVE (more effective than placebo)** Diazepam is more effective than placebo for neurosis or psychosomatic disease	**EFFECTIVE, BUT LONG TERM TREATMENT NOT RECOMMENDED DUE TO POTENTIAL ADVERSE EVENTS**
COMMENTS	The focus of this study was on depression	Only Japanese studies were included.	The focus of this study was on geriatric anxiety disorders and also looked at studies of cognitive behavioural interventions This review also Included studies of cognitive behavioural interventions and pharmacological interventions not relevant to our question

**for some SRs the numbers of studies for each benzodiazepine do not add up to the total number of relevant studies, as some trials studied more than one type of benzodiazepine.*

KEY: Benzo/s = Benzodiazepine/s

AMSTAR TABLE

Table 4. AMSTAR[4] rating of included systematic reviews

AMSTAR checklist items	Gould 1997(5)	Hidalgo 2007(6)	Mahe 2000(7)	Martin 2007(8)	Mitte 2005(9)	Cox 1992(10)	Watanabe 2009(11)	Furukawa 2001(12)	Inada 2003(13)	Wethrell 2005(14)
1. Was an 'a priori' design provided?	No	Yes	No	No	No	Can't answer	Yes	Yes	No	No
2. Was there duplicate study selection and data extraction?	Can't answer	Yes	Yes	Can't answer	Yes	Can't answer	Yes	Yes	No	Can't answer
3. Was a comprehensive literature search performed?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	Yes	No	Yes	Yes	Can't answer	Yes	Yes	No	Can't answer
5. Was a list of studies (included and excluded) provided?	No	No	No	No	No	No	Yes	Yes	No	No
6. Were the characteristics of the included studies provided?	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
7. Was the scientific quality of the included studies assessed and documented?	No	No	No	Yes	Yes	No	Yes	Yes	Yes	No
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	No	No	No	Yes	Yes	No	Yes	Can't answer	Yes	Yes
9. Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Can't answer	Yes	Yes	Yes	Yes	Yes	No	N/A
10. Was the likelihood of publication bias assessed?	No	Yes	No	Yes	Yes	No	Yes	Yes	No	N/A
11. Was the conflict of interest included?	No	No	No	No	No	No	No	No	No	Can't answer
AMSTAR score	4/11	5/11	2/11	6/11	8/11	2/11	10/11	9/11	3/11	5/11

DISCLAIMER

The information in this report is a summary of that available and is primarily designed to give readers a starting point to consider currently available research evidence. Whilst appreciable care has been taken in the preparation of the materials included in this publication, the authors and the National Trauma Research Institute do not warrant the accuracy of this document and deny any representation, implied or expressed, concerning the efficacy, appropriateness or suitability of any treatment or product. In view of the possibility of human error or advances of medical knowledge the authors and the National Trauma Research Institute cannot and do not warrant that the information contained in these pages is in every aspect accurate or complete. Accordingly, they are not and will not be held responsible or liable for any errors or omissions that may be found in this publication. You are therefore encouraged to consult other sources in order to confirm the information contained in this publication and, in the event that medical treatment is required, to take professional expert advice from a legally qualified and appropriately experienced medical practitioner.

CONFLICT OF INTEREST

The TAC/WSV Evidence Service is provided by the National Trauma Research Institute. The NTRI does not accept funding from pharmaceutical or biotechnology companies or other commercial entities with potential vested interest in the outcomes of systematic reviews.

The TAC/WSV Health Services Group has engaged the NTRI for their objectivity and independence and recognise that any materials developed must be free of influence from parties with vested interests. The Evidence Service has full editorial control.

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APPENDIX 1: EXPANDED SUMMARY TABLES

Table A1.1 Systematic reviews of benzodiazepines for Generalised Anxiety Disorder

STUDY	Gould 1997(5)	Hidalgo 2007(6)	Mahe 2000(7)	Martin 2007(8)	Mitte 2005(9)
AMSTAR RATING	4/11	5/11	2/11	6/11	8/11
BENZODIAZEPINES*					
Alprazolam	3 studies	1 study	1 study	4 studies	6 studies
Bromazepam	3 studies				3 studies
Clobazam	1 study		1 study		
Diazepam	8 studies	1 study	7 studies	12 studies	13 studies
Flunitrazepam					
Lorazepam	5 studies	2 studies	3 studies	7 studies	7 studies
Midazolam					
Nitrazepam					
Oxazepam					
Temazepam					
Triazolam					1 study
PATIENTS	Patients with GAD (APA DSM-III, DSM-IIIR, or DSM-IV) or patients who clearly would have met the above criteria if they had been applied	Patients with GAD (DSM-III-R, DSM-IV and ICD-10)	"patients with conditions described as generalised anxiety disorder, anxiety neurosis or anxiety symptoms"	Patients with GAD (DSM-IV, DSM-III or DSM-III-R) **Excluded:** patients with psychiatric disorders or who were consuming or dependent on substances of abuse or with other medical problems.	Patients with GAD (any diagnostic system), or an exact description of the disorder was presented including duration of symptoms (i.e. insufficient if patients just described as 'anxious' or "neurotic")
OUTCOMES	Measure of anxiety or worry & measure of depression (effect size)	Measure of anxiety (effect size)	Benefits to patients/ successful long-term treatment of anxiety Measure of anxiety	**Efficacy:** as measured by withdrawals from study **Side effects:** as measured by withdrawals due to adverse events	Self-report, observer rated measures, or behavioural test of anxiety, depression, quality of life, or clinical significance (only pertaining to anxiety).

STUDY	Gould 1997(5)	Hidalgo 2007(6)	Mahe 2000(7)	Martin 2007(8)	Mitte 2005(9)
COMPARATORS OF INTEREST	**Pharmacotherapy vs Placebo** Total included drug studies (n=22) **Relevant benzo studies (n= 17)** Alprazolam vs placebo (n=3) Castillo (1987), Enkelmann (1991), Fontaine (1984) Bromazepam vs placebo (n=3) Fontaine (1986), Fontaine (1984), Kragh-Sorensen (1990) Clobazam vs placebo (n=1) Castillo (1987) Diazepam vs placebo (n=8) Borison (1990), Cohn (1989), Fontaine (1987), Olajide (1987), Pecknold (1989), Rickels (1993), Rickels (1982), Ross & Matas (1987) Lorazepam vs placebo (n=5) Ansseau (1985), Ceulmans (1985), Cutler (1993), Diamond (1991), Fontaine (1986) other drug studies (n=5) *n.b. some benzo vs placebo studies also looked at other drugs vs placebo, some studies looked at more than one drug vs placebo*	**Pharmacotherapy vs Placebo** Total included studies (n=21) **Relevant benzo studies (n= 4)** Alprazolam vs placebo (n=1) Moller (2001) Lorazepam vs placebo (n=2) Pande (2003), Feltner (2003) Diazepam, placebo (n=1) Hackett (2003) **other drug studies (n=22)** SSRI studies (n=8) venlafaxine studies (SNRI) (n=5) hydroxyzine studies (AH) (n=3) PGB studies (n=2) buspirone arms (n=2) complementary and alternative medicine studies (n=2) *n.b. some benzo vs placebo studies also looked at other drugs vs placebo, some studies looked at more than one drug vs placebo*	**Various** Total included studies (n=13) **Total GAD studies (n=8)** **Relevant benzo studies (n= 4)** Alprazolam vs placebo, lorazepam vs placebo (n=1) Cohn & Wilcox (1984) Diazepam vs placebo (n=1) Power (1990) Buspirone vs diazepam (n=1) Murphy (1989) Diazepam, no comparator (n=1) Rickels (1983) **Total non well-defined anxiety disorder studies (n=5)** **Relevant benzo studies (n=4)** Clobazam vs diazepam (n=1) Schjonsby (1979) Ketazolam vs diazepam (n=1) Fabre (1981) Lorazepam, diazepam; open label (n=1) Siassi (1975) Lorazepam, diazepam; open label (n=1) Gross (1977) *n.b. some benzo vs placebo studies also looked at other drugs vs placebo, some studies looked at more than one drug vs placebo*	**Benzodiazepine vs placebo** Total included studies (n=23) **Relevant benzo studies (n= 23)** diazepam vs placebo (n=12) lorazepam vs placebo (n=7) alprazolam vs placebo (n=4) Included studies: Andreatini (2002), Ansseau (1991), Boyer (1993), Castillo (1987), Cutler (1993), Diamond (1991), Enkelmann (1991), Feltner (2003), Fontaine (1983), Fontaine(b) (1986), Hackett (2003), Laakmann (1998), Loo (1991), Lydiard (1997), Moller (2001), Pande (2003), Pecknold (1985), Pecknold(b) (1989), Poumotabbed (1996), Rickels (1993), Rickels(b) (1997), Rickels(c) (2000), Zung (1986) *n.b. specific benzo used in each study not stated*	**Pharmacotherapy vs placebo** Total included studies (n=48) **Relevant benzo studies (n=25)** Alprazolam vs placebo (n=6) Castillo (1987), Cohn & Wilcox (1984), Enkelmann (1991), Lydiard (1997), McLeod (1982), Moller (2001) 'Benzodiazepines' (bromazepam, diazepam) (n=1) Fontaine (1984) Bromazepam vs placebo (n=2) Fontaine (1983), Fontaine (1986) Diazepam vs placebo (n=12) Boyer & Feighner (1993), Fontaine (1983), Fontaine (1987), Goldberg & Finnerty (1982), Pecknold (1989), Pourmotabbed (1996), Power (1989), Power (1990), Rickels (1982), Rickels (1993), Rickels (1997), Rickels (2000) Lorazepam vs placebo (n=6) Cohn & Wilcox (1984), Cutler (1993), Fontaine (1986), Fresquet (2000), Laakmann (1998), Laboratorios Dr Esteve* (unpublished) Triazolam vs placebo (n=1) Fontaine (1990) *n.b. some benzo vs placebo studies also looked at other drugs vs placebo, some studies looked at more than one drug vs placebo*
DURATION OF TREATMENT	Not specified in selection criteria for SR. Duration of treatment for included studies varied between 2 and 9 weeks	Not specified in selection criteria for SR. Duration of treatment for included studies varied between 4 and 12 weeks	Long-term (8 weeks or longer)	Not specified in selection criteria for SR. Conclusions drawn for short-term treatment. "the trials were conducted in the very short-term, with most lasting just 4 weeks" Individual trial durations were not specified	Selection criteria for SR specified a minimum of 14 days treatment The average duration of the included benzo studies was 5.3 weeks. "Four studies investigated the drug for less than 4-weeks, however, effect sizes for those studies were comparable with studies in which the drugs were investigated for a longer period of time" Recommendations were made against long-term use due to the increasing risk of dependence and withdrawal reported elsewhere.
RESULTS	Benzodiazepines:	Benzodiazepines:	No overall effect size or result	Pooled analysis indicated less risk of	For benzodiazepines, the mean effect

STUDY	Gould 1997(5)	Hidalgo 2007(6)	Mahe 2000(7)	Martin 2007(8)	Mitte 2005(9)
	Mean ES = 0.70 Diazepam (11 studies): ES=0.76 Lorazepam (5 studies): ES=0.66 Alprazolam & bromazepam (2 studies each); ES=0.44 & 0.61 "Among medication interventions, the benzodiazepine diazepam yielded the largest effect size (ES=0.76), followed by lorazepam (ES=0.66)"	ES±SD = 0.38+0.15 p-Value = *p*<0.0001 "Our analysis showed a low to moderate overall ES (0.39+0.06) for drug therapy in the treatment of GAD... On the higher end of the spectrum we found the anticonvulsant PGB and the AH hydroxyzine, followed in order by venlafaxine XR, BZs and SSRIs"	calculated, or conclusions drawn about any specific benzidoazepines, or benzodiazepines as a whole "the results of the reported long-term studies in patients with GAD are inconclusive, and no reference drug has shown to be effective in the long-term treatment of this condition... although long-term treatment of generalized anxiety disorder is an unmet medical need, no reference drug has yet been identified, nor has an adequate treatment evaluation of this condition been performed"	treatment discontinuation due to lack of efficacy for benzodiazepines, compared to placebo, RR=0.29 (95% CI 0.18–0.45; *p*<0.00001). Nevertheless, pooled analysis showed no conclusive results for risk of all-cause patient discontinuation, RR=0.78 (95% CI 0.62–1.00; *p*=0.05). "the outcomes observed in this review seem to show that, based on total withdrawals from clinical studies, benzodiazepines do not even prove definitively superior to placebo in the short term. In a clinical (though not experimental) setting, subjects could withdraw from treatment a few weeks after the start in the same proportions as subjects who receive a placebo in a clinical trial, indicating that benzodiazepines are not an effective treatment for GAD"	size for anxiety was *g* = 0.32. There was no significant difference between drug classes. For depression the mean effect size for benzodiazepines was *g* = 0.28. Again no drug class was superior "Our findings indicate that pharmacotherapy is an effective treatment for GAD in reducing both anxiety and comorbid depressive symptoms; superiority over placebo was given. According to drug classes, no differences in efficacy but in compliance were found. So, results suggest that benzodiazepines are to be preferred at least when the duration of the treatment is short"
CONCLUSIONS	**EFFECTIVE** **(more effective than placebo)** Benzos in order of effectiveness from most to least: Diazepam, Lorazepam, Bromazepam, Alprazolam	**EFFECTIVE (low to moderate)** Order of effectiveness (most to least): Pregabalin, Hydroxyzine, Venlafaxine SR, Benzos, SSRIs, Buspirone, complementary and alternative meds	**INCONCLUSIVE** Evidence of effectiveness is inconclusive	**NOT EFFECTIVE** **(not more effective than placebo)** Benzos are not effective for the short-term treatment of GAD (no difference between benzos and placebo)	**EFFECTIVE** **(more effective than placebo)** Benzos and azapirones equally effective, both classes of drug more effective than placebo for short-term treatment
COMMENTS	This meta-analysis looked at pharmacotherapy and CBT for GAD, benzodiazepines were only part of the results. The authors note that "the long-term efficacy of pharmacologic treatment was attenuated following medication discontinuation" As well as looking at pharmacotherapy vs placebo, this review also looked at psychological treatments vs control (n=13)	No individual effect sizes reported for the different benzodiazepines used in the included studies, just a combined overall effect size for benzodiazepines A study of bromazepam (*Llorca (2002*) was included in the review, but efficacy data was not reported and not included in the analysis	This review looks at long-term treatment of GAD (8 weeks or longer) As well as treatment for non well-defined anxiety disorder (n=5 studies) This review also looks at different types of pharmacotherapy – not just benzos. The authors state that benzos are not recommended long-term due to the risk of dependence	"We chose withdrawals from trials for any reason as the principal outcome measure in this review, as was done in the recently published large trial in schizophrenia called CATIE (Lieberman *et al.*, 2005). We argue that withdrawal for any reason represents the most comprehensible and comprehensive overall index of effectiveness of any intervention."	This review looked at benzos vs placebo,and azapirones vs placebo and then compared effect sizes The authors state that "it is known that there is an increasing risk of physical dependence and withdrawal after long-term treatment with benzodiazepines...In addition, other severe adverse effects can result from long-term use...such as impairment of memory. Therefore prescriptions should be limited to short-term use"

**for some SRs the numbers of studies for each benzodiazepine do not add up to the total number of relevant studies, as some trials studied more than one type of benzodiazepine.*

KEY: GAD = Generalised Anxiety Disorder Benzo/s = Benzodiazepine/s SSRIs = Selective Serotonin Reuptake Inhibitors

Table A1.2 Systematic reviews of benzodiazepines for Panic Disorder

STUDY	Cox 1992(10)	Watanabe 2009(11)
AMSTAR RATING	2/11	10/11
BENZODIAZPINES*		
Alprazolam	✓#	2 studies
Bromazepam		
Clobazam		
Diazepam		1 study
Flunitrazepam		
Lorazepam		
Midazolam		
Nitrazepam		
Oxazepam		
Temazepam		
Triazolam		
PATIENTS	Patients with panic disorder or panic disorder with agoraphobia (agoraphobia with panic attacks in DMS-III). "Only studies that specifically stated they contained a large percentage of subjects with both panic attacks and agoraphobic avoidance were included."	Adult patients with panic disorder with or without agoraphobia (Feighner criteria, Research Diagnostic Criteria, DSM-III, DSM-III-R, DSMIV or ICD-10)
OUTCOMES	1/ Dysphoria or depression 2/ Frequency of panic attacks per week 3/ Severity of panic attacks 4/ Agoraphobic fear 5/ Agoraphobic avoidance behaviour 6/ Generalized anxiety 7/ Overall improvement ratings	***"Primary outcome(s):*** "Response" (a dichotomised outcome) in each arm, defined by global judgement of the original authors, such as: "very much" or "much" improvement, "no or minimal" symptom, or a Panic Disorder Severity Scale (PDSS) score of 7 or below. ***Secondary outcome(s):*** 1. Panic disorder global severity on a continuous scale 2. Frequency or severity of panic attacks 3. Phobic avoidance 4. General anxiety 5. Depression 6. Social functioning 7. Quality of life 8. Patient satisfaction with treatment 9. Economic costs"
COMPARATORS OF INTEREST	This meta-analysis calculated and compared effect sizes of alprazolam, Imipramine and exposure therapy Included studies (n=34) #No list or details of included studies were provided, therefore, it was not possible to list the included studies determine the number of studies of alprazolam or determine the comparators used in these	**benzos + psychotherapy vs (psychotherapy alone or benzo treatment)** Total included studies (n=3) **Total relevant studies (n=3)** Irrelevant studies (n=0) <u>Alprazolam + CBT vs Placebo pill + CBT (n=1)</u> Auerbach (1997) <u>alprazolam vs alprazolam+exposure vs double placebo vs exposure (n=1)</u> Marks (1993) <u>Diazepam + Exposure vs Placebo pill + Exposure (n=1)</u> Wardle (1994)
RESULTS	"Few studies satisfied the minimum criteria of inclusion and the final data pool consisted of 34 treatment studies. Imipramine was found to be generally ineffective for most variables. Alprazolam was significantly effective for panic and anxiety variables in PDA, while exposure was significantly for phobia variables. Exposure had the most consistently strong effect sizes." "The results of the meta-analysis indicate that alprazolam and exposure therapies are both effective for PDA, but alprazolam was not effective for agoraphobic dimensions. Imipramine was found to be generally effective"	"Two trials (n=166) compared combination with psychotherapy alone (both using behaviour therapy).No statistically significant differences were observed in response during the intervention (relative risk (RR) for combination 1.25, 95% CI 0.78 to 2.03, P = 0.35), at the end of the intervention (RR 0.78, 0.45 to 1.35, P = 0.37), or at the last follow-up time point Follow-up data suggested that the combination might be inferior to behaviour therapy alone (RR 0.62, 0.36 to 1.07, P = 0.08). One trial (n=77) compared combination with a benzodiazepine alone. No differences were found in response during the intervention (RR 1.57, 0.83 to 2.98, P = 0.17). Although the combination appeared to be superior to the benzodiazepine alone at the end of treatment (RR 3.39, 1.03 to 11.21, P = 0.05). No significant differences were observed at the 7-month follow-up (RR 2.31, 0.79 to 6.74, P = 0.12)." "The review established the paucity of high quality evidence investigating the efficacy of psychotherapy combined with benzodiazepines for panic disorder. "Currently, there is inadequate evidence to assess the clinical effects of psychotherapy combined with benzodiazepines for patients who are diagnosed with panic disorder."
CONCLUSIONS	**EFFECTIVE** Alprazolam and exposure therapies both effective for PDA	**INSUFFICIENT EVIDENCE** Insufficient evidence to assess clinical effects of benzodiazepines

	Alprazolam was significantly effective for panic and anxiety variables in PDA, while exposure was significantly effective for phobia variables. Exposure had the most consistently strong effect sizes Alprazolam was not effective for agoraphobic dimensions	+ psychotherapy for panic disorder
COMMENTS		See article for details on the scales used to measure the different outcomes of the study.

**for some SRs the numbers of studies for each benzodiazepine do not add up to the total number of relevant studies, as some trials studied more than one type of benzodiazepine.*

KEY: PDA = Panic Disorder with Agoraphobia Benzo/s = Benzodiazepine/s

Table A1.3 Systematic reviews of benzodiazepines for other types of anxiety

STUDY	Furukawa 2001(12)	Inada 2003(13)	Wethrell 2005(14)
AMSTAR RATING	9/11	3/11	5/11
TYPE OF ANXIETY	anxiety associated with major depression	neurosis or psychosomatic disease	any anxiety disorder
BENZODIAZEPINES*			
Alprazolam	1 study	1 study	1 study
Bromazepam			
Clobazam		2 studies	
Diazepam	1 study	17 studies	
Flunitrazepam	1 study		
Lorazepam		1 study	
Midazolam			
Nitrazepam			
Oxazepam			
Temazepam			
Triazolam	1 study		
PATIENTS	**anxiety associated with major depression** adults (aged 18 or older) with major depression, diagnosed according to any one of the Feighner criteria, RDC, DSM-III, DSMIII- R orDSM-IV, or ICD-10. Comorbidities with anxiety disorders included.	"The subjects were all Japanese patients suffering from **neurosis** or **psychosomatic disease**, as diagnosed according to the Japanese diagnostic system based on ICD-9... More recently, subjects were selected based on operational diagnostic criteria such as ICD-10 or DSM-IV"	participants were at least 55 years old, with a principal or co-principal diagnosis of any anxiety disorder diagnosed according to criteria of the Diagnostic and Statistical Manual of Mental Disorders III-R or IV
OUTCOMES	**Primary outcome**: Depressive severity, (at least one measure) Symptom severity could be measured by either self-report or observer-rating **Secondary outcomes**: 1. Response in depression; 2. Acceptability of treatment; 3. Anxiety severity; 4. Insomnia severity; 5. Side effects	Final Global Improvement Rating scale (FGIR) used to capture "changes in the overall severity of patient symptoms" expressed as a Relative Risk after meta-analysis	To compare clinical significance across studies, effect sizes were calculated where possible for each outcome measure (including: CGI, Clinical Global Impression; HAMA, Hamilton Anxiety Scale; STAI, Spielberger State-Trait Anxiety Inventory; VAS, Visual Analogue Scale) within each study.
COMPARATORS OF INTEREST	Antidepressants + benzos vs antidepressants alone Total Included studies (n=10) Relevant included studies (n= 4) imipraime + triazolam vs imipramine (n=1) Dominguez (1984) desipramine + alprazolam vs desipramine (n=1) Fawcett (1987) imipramine + diazepam vs imipramine (n=1) Feet (1985) (maprotiline or nortriptyline) + (flunitrazepam or lormetazepam) vs (maprotiline or nortriptyline) (n=1) Nolen (1993b)	Benzo vs diazepam vs placebo (both diazepam and placebo were used as controls in all included studies) Total Included studies (n=17) Relevant included studies (n= 17) Alprazolam vs diazepam vs placebo (n=1) Ito (1982) Clobazam vs diazepam vs placebo (n=2) Kudo (1982), Mori (1982) Lorazepam vs diazepam vs placebo (n=1) Ito (1981) Other drug vs diazepam vs placebo (n=13) Hada (1979), Higuchi (1975), Ichimaru (1970), Ito (1981), Kudo (1984), Kudo (1983), Kurihara (1992), Kurihara (1990), Kurihara (1977), Mori (1977), Namiki (1974), Suematsu (1975), Suzuki (1979)	Benzo vs antidepressant vs placebo Total included pharmalogical studies (n=8) Relevant included studies (n=1) Imipramine vs alprazolam vs placebo (n=1) Sheikh & Swales (1999) pilot RCT
RESULTS	"The results suggest the superiority of the combination therapy in alleviating anxiety even up to six to eight weeks, with statistically significant SMDs between -0.50 and - 0.64."	"Meta-analysis of the total 17 RCTs demonstrated diazepam to be significantly more effective than placebo in the treatment of neurosis or psychosomatic disease (relative risk 1.35, 95% CI 1.21–1.51, number needed to treat 9)... The effectiveness of diazepam was particularly notable at a maximum dose of 12 mg/day or higher, while no significant superiority compared with the placebo was observed at a dose of 9 mg/day or lower."	"only three randomized controlled trials have investigated the impact of benzodiazepines for anxiety disorders in later life. Two of these trials have focused on GAD, and one trial has studied an earlier, potentially comparable category of anxiety neurosis. In all of these studies, medication was efficacious relative to placebo, with treatment effects evident within as early as 7 days. Only one study provided sufficient data for the calculation of effect size, with *d* ranging from 0.79 to 0.95 (mean *d*, .85). Response rates to medication ranged from 57% to 83%. Attrition rates were

			generally low (%17%)."
CONCLUSIONS	**EFFECTIVE, BUT BENEFITS SHOULD BE WEIGHED AGAINST RISKS**	**EFFECTIVE (more effective than placebo)** "Results of the metaanalysis of the 17 RCTs selected in this study suggest that diazepam is significantly more effective than the placebo in the treatment of neurosis or psychosomatic disease."	**EFFECTIVE, BUT LONG TERM TREATMENT NOT RECOMMENDED DUE TO POTENTIAL ADVERSE EVENTS**
COMMENTS	**The focus of this study was on depression** **The authors state that:** "The potential benefits of adding a benzodiazepine to an antidepressant must be balanced judiciously against possible harms including development of dependence and accident proneness, on the one hand, and against continued suffering following no response and drop out, on the other."	Only Japanese studies were included.	The focus of this study was on geriatric anxiety disorders and also looked at studies of cognitive behavioural interventions This review also Included studies of cognitive behavioural interventions and pharmacological interventions not relevant to our question**The authors state that:** "Overall, the data from these trials suggest the value of benzodiazepines for treating anxiety disorders in older adults, However, longer-term treatment with benzodiazepines generally is not recommended, particularly for older adults, given the potential for more serious adverse events. Benzodiazepines can affect cognitive functioning and psychomotor performance, leading to an increased risk of hip fractures caused by falls, a decreased ability to drive, and an increase in memory problems."

**for some SRs the numbers of studies for each benzodiazepine do not add up to the total number of relevant studies, as some trials studied more than one type of benzodiazepine.*

KEY: Benzo/s = Benzodiazepine/s

APPENDIX 2: EVIDENCE MAP SUMMARY

The TAC and WorkSafe Victoria requested an Evidence Review on the use of sedatives in anxiety, insomnia and muscle spasm. This proved to be an unfeasibly large topic with so many different combinations of drugs and conditions needing investigation. It was decided that instead, an evidence map would be developed as a first step to identify the available higher level evidence and get an idea of its quantity and complexity. An evidence map of systematic reviews and evidence-based guidelines on hypnosedatives for anxiety, insomnia and muscle spasm was developed(3). Drugs classed as 'hypnosedatives' for the purposes of the evidence map were those licensed for use in Australia and listed in MIMs as either 'anti-anxiety agents' or 'sedatives, hypnotics' (see Table A2.1)

Table A2.1. hypnosedatives included in Evidence Map

Benzodiazepines	Non-benzodiazepine Hypnotics
Alprazolam	Zolpidem
Bromazepam	Zopiclone
Clobazam	
Diazepam	
Flunitrazepam	
Lorazepam	
Midazolam	
Nitrazepam	
Oxazepam	
Temazepam	
Triazolam	

Searches of Medline and Embase, and the internet yielded 1,943 potentially relevant studies. Screening against inclusion and exclusion criteria resulted in a total of 41 relevant studies (34 systematic reviews [SRs] and 7 evidence-based guidelines [EBGs]). See Appendix 3 for detailed search methodology and selection criteria.

For included studies, the following data was extracted

- Study type (systematic review or evidence based guideline)
- Hypnosedatives examined
- Indication
- Whether the study was about benefits, harms or both

The extracted data was tabulated in evidence maps to allow determination of the volume of existing evidence, and identify the gaps. No quality appraisal was undertaken in the production of the Evidence Map.

There were 18 SRs and 5 EBGs on hypnosedatives for anxiety; 17 SRs and 2 EBGs for insomnia; and 1 SR for muscle spasm. There were no EBGs on hypnosedatives for muscle spasm (Table A1.2). The total number of SRs identified (34) is less than the sum of SRs for the individual indications (36) as one SR covered all three indications.All other guidelines and systematic reviews were about one indication only.

Table A2.2. Evidence map for each indication

Indication	Systematic Reviews	Evidence Based Guidelines

Anxiety	18	5
Insomnia	17	2
Muscle spasm	1	0

The benzodiazepines listed in the research question are those used in Australia, however, many studies included various other benzodiazepines (i.e. studies from the UK or US often only included benzodiazepines licensed for use in that country). This should be kept in mind when looking at recommendations or reported results for 'benzodiazepines', as the list of drugs that different authors are referring to are not likely to be the same. Further detail about the evidence identified (i.e. such as specific indications or individual drugs included in each study), see Evidence Map report(3).

APPENDIX 3: EVIDENCE MAP METHODS

Inclusion and exclusion criteria

Inclusion and exclusion criteria were established a priori (Table A3.1) and were applied by two reviewers. Any discrepancies were discussed and resolved.

Table A3.1. Inclusion and exclusion criteria

Patient/ population	**Inclusion**: patients with: • Anxiety (including anxiety disorders) • Insomnia, or • Muscle spasm All ages
	Exclusion: Conditions occurring in the context of cancer, Stiff Man Syndrome, Athetosis, Alcohol withdrawal, Tetanus, Status epilepticus, Allergy treatment (urticaria, pruritis), Spasticity due to upper motor neuron lesion, Migraine, Dementia, Bipolar disorder, Schizophrenia, Psychosis, Neurodegenerative disorders, Delirium, Borderline personality disorder, Dyspnoea, Detoxification or withdrawal from benzodiazepine addiction. Patients receiving sedatives for the following purposes: preoperative medication, induction of anaesthesia, sedation in intensive care unit, as an antiemetic.
Intervention/ indicator	**Inclusion:** Studies where the focus is at least one of the following hypnosedatives: Benzodiazepines Alprazolam, Bromazepam, Clobazam, Diazepam, Flunitrazepam, Lorazepam, Midazolam, Nitrazepam, Oxazepam, Temazepam, Triazolam Non-benzodiazepine Hypnotics Zolpidem, Zopiclone
	Exclusion: Studies where the included hypnosedatives were only reported on as a comparator
Comparison/ control	**Inclusion:** Any
	Exclusion: Nil
Outcomes	**Inclusion:** Outcomes related to resolution or reduction of problem being treated. Outcomes related to the effect of treatment on function (ability to conduct daily activities), QOL, other medication use, return to work. Adverse effects
	Exclusion: studies on pharmacokinetics
Setting	**Inclusion:** All health care settings not on the exclusion list (e.g. acute, primary care, rehabilitation)
	Exclusion: • Intensive care unit • Nursing homes • Palliative care
Study design	**Inclusion:** Evidence-based guidelines or Systematic reviews
	Exclusion: Non-EBGs, non-systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies, case-control studies, case series, editorials, letters, commentaries.
Publication details	**Inclusion:** Studies in English and conducted on humans
	Exclusion: Studies in languages other than English and/or conducted on animals
Time period	**Inclusion:** Any publication date
	Exclusion: Nil

For a study to be included, at least one of the hypnosedatives had to be specified in the search strategy to ensure that all references about that drug were sought. Where an included drug was not the focus of the study, but results of the drug as a comparator were reported, the study was excluded.

Data extraction

Data on characteristics of the studies were extracted and summarised for evidence mapping.

Search strategy

A highly sensitive search in Medline and Embase as detailed below was undertaken for all the generic and Australian product drug names to be reviewed. A further highly sensitive filter for synthesized evidence was applied and the results limited to those in English. The larger Embase yield was further reduced by limiting the results to the three conditions under review; anxiety, insomnia and muscle spasm.

Table A3.2. Databases accessed

Database name	Dates covered	Date searched	Refs
Embase	1980 to 2010 Week 04	05/02/2010	1,444
Medline	1950 to January Week 3 2010	05/02/2010	595
TOTAL			1,921

Table A3.3. Search strategies used

Database name	Strategy
Embase	1. exp Anxiety/ 2. (anxiety or anxious).ti,ab. 3. or/1-2 4. exp "Sleep Initiation and Maintenance Disorders"/ 5. (insomnia or sleep*).ti,ab. 6. or/4-5 7. exp Spasm/ 8. ((muscular or muscle*) adj5 spasm*).ti,ab. 9. or/7-8 10. Alprazolam/ 11. (Alprax or Alprazolam or Kalma or Xanax or Xanax or Zamhexal).ti,ab. 12. or/10-11 13. Bromazepam/ 14. Lexotan.ti,ab. 15. or/13-14 16. (Clobazam or Frisium).ti,ab. 17. Diazepam/ 18. (Antenex or Diazepam or Ducene or Ranzepam or Valium or Valpam).ti,ab. 19. or/17-18 20. Flunitrazepam/ 21. Hypnodorm.ti,ab. 22. or/20-21

	23. Lorazepam/ 24. Ativan.ti,ab. 25. or/23-24 26. Midazolam/ 27. Hypnovel.ti,ab. 28. or/26-27 29. Nitrazepam/ 30. (Alodorm or Mogadon).ti,ab. 31. or/29-30 32. Oxazepam/ 33. (Alepam or Murelax or Serepax).ti,ab. 34. or/32-33 35. Temazepam/ 36. (Temazepam or Normison or Temaze or Temtabs).ti,ab. 37. or/35-36 38. Triazolam/ 39. Halcion.ti,ab. 40. or/38-39 41. (Zolpidem tartrate or Dormizol or Somidem or Stildem or Stilnox or Zolpibell or Zolpidem).ti,ab. 42. (Zopiclone or Imovane or Imrest).ti,ab. 43. or/12,15-16,19,22,25,28,31,34,37,40-42 44. hypnosedative*.ti,ab. 45. 43 or 44 46. "review"/ or review.pt. or review.ti. 47. (systematic or evidence$ or methodol$ or quantitativ$ or analys$ or assessment$).ti,sh,ab. 48. 46 and 47 49. Meta-Analysis/ 50. meta-analysis.mp. 51. "systematic review"/ 52. (meta-analy$ or metanaly$ or metaanaly$ or meta analy$).mp. 53. ((systematic$ or evidence$ or methodol$ or quantitativ$) adj5 (review$ or survey$ or overview$)).ti,ab,sh. 54. ((pool$ or combined or combining) adj2 (data or trials or studies or results)).ti,ab. 55. or/48-54 56. exp practice guideline/ 57. (clinical adj3 guideline*).ti,ab. 58. or/55-57 59. 45 and 58 60. 3 and 59 61. 6 and 59 62. 9 and 59 63. 60 or 61 or 62 English articles only
Medline	1. "review"/ or review.pt. or review.ti. 2. (systematic or evidence$ or methodol$ or quantitativ$ or analys$ or assessment$).ti,sh,ab. 3. 1 and 2 4. meta-analysis.pt. 5. Meta-Analysis/ 6. "systematic review*".ti,ab.

	7. (meta-analy$ or metanaly$ or metaanaly$ or meta analy$).mp. 8. ((systematic$ or evidence$ or methodol$ or quantitativ$) adj5 (review$ or survey$ or overview$)).ti,ab,sh. 9. ((pool$ or combined or combining) adj2 (data or trials or studies or results)).ti,ab. 10. practice guideline/ 11. (clinical adj3 guideline*).ti,ab. 12. or/3-11 13. Alprazolam/ 14. (Alprax or Alprazolam or Kalma or Xanax or Xanax or Zamhexal).ti,ab. 15. or/13-14 16. Bromazepam/ 17. Lexotan.ti,ab. 18. or/16-17 19. (Clobazam or Frisium).ti,ab. 20. Diazepam/ 21. (Antenex or Diazepam or Ducene or Ranzepam or Valium or Valpam).ti,ab. 22. or/20-21 23. Flunitrazepam/ 24. Hypnodorm.ti,ab. 25. or/23-24 26. Lorazepam/ 27. Ativan.ti,ab. 28. or/26-27 29. Midazolam/ 30. Hypnovel.ti,ab. 31. or/29-30 32. Nitrazepam/ 33. (Alodorm or Mogadon).ti,ab. 34. or/32-33 35. Oxazepam/ 36. (Alepam or Murelax or Serepax).ti,ab. 37. or/35-36 38. Temazepam/ 39. (Temazepam or Normison or Temaze or Temtabs).ti,ab. 40. or/38-39 41. Triazolam/ 42. Halcion.ti,ab. 43. or/41-42 44. (Zolpidem tartrate or Dormizol or Somidem or Stildem or Stilnox or Zolpibell or Zolpidem).ti,ab. 45. (Zopiclone or Imovane or Imrest).ti,ab. 46. or/15,18-19,22,25,28,31,34,37,40,43-45 47. hypnosedative*.ti,ab. 48. 46 or 47 49. 12 and 48 English articles only

Website searches to identify relevant evidence-based guidelines

The reviewers were aware of websites of guideline clearinghouses, guideline developers, centres of evidence-based practice, Australian government health services and websites of specific relevance (eg. accident compensation groups) known to contain evidence-based resources.

The 17 websites previously identified by the review team (9 guideline services, 2 Australian government websites and 1 centre of evidence-based practice, and 5 other accident commission websites) were searched for relevant EBGs. Details of websites searched can be found in Table A1.4.

Where an internal search engine was available, websites were searched using the search strings detailed in the table below. If no search engine was available, lists of EBGs, publications or other resources identified on the site were scanned for relevant documents.

Table A3.4. Websites searched to identify relevant guidelines

Guideline Services	
National Institute of Clinical Studies. Clinical Practice Guidelines Portal http://www.clinicalguidelines.gov.au/	Web page reviewed: Guideline Portal, Browse by condition
National Health and Medical Research Council (NHMRC) www.nhmrc.gov.au	Web page reviewed: Guidelines, health
National Institute for Health and Clinical Excellence UK (NICE) www.nice.org.uk	Web page reviewed: Our guidance, health topic, Mental health and behavioural conditions Web page reviewed: Our guidance, health topic, Musculoskeletal
New Zealand Guideline Group (NZGG) www.nzgg.org.nz	Web page reviewed: Guidelines and Reports
Scottish Intercollegiate Guidelines Network (SIGN) www.sign.ac.uk	Web page reviewed: Guidelines Mental Health Web page reviewed: Guidelines Other
Guidelines International Network www.g-i-n.net *(members only)*	Web page reviewed: International Guideline Library Searched by keywords: sedative, sedatives*, anxiety, sleep OR insomnia, muscle, spasm, Alprazolam OR bromazepam OR clobazam OR diazepam OR flunitrazepam OR lorazepam OR midazolam OR nitrazepam OR oxazepam OR temazepam OR triazolam OR zolpidem OR zopiclone
Guidelines Advisory Committee www.gacguidelines.ca	Web page reviewed: List all topics and summaries
National Guideline Clearinghouse US (NGC) www.guidelines.gov	Searched by: **Keyword:** *(Alprazolam OR Bromazepam OR Clobazam OR Frisium OR Diazepam OR Flunitrazepam OR Lorazepam OR Midazolam OR Nitrazepam OR Oxazepam OR Temazepam OR Triazolam OR Zopiclone or Imovane or Imrest)* **Disease/Condition:** *(trauma OR spinal OR spine OR brain OR anxiety OR sleep OR insomnia OR muscle OR muscular)*)
TRIP Database www.tripdatabase.com	Searched by: Drug names
Australian Government Websites containing Guidelines	
Australian Government Department of Health and Ageing www.health.gov.au	Web page reviewed: Health Professionals – Treatments & Techniques – Guidelines
NSW Health www.health.nsw.gov.au	Web page reviewed: Publications & Resources – Policy Directives and Guidelines
Centres of Evidence Based Practice Websites	
WA Centre for Evidence Based Nursing and Midwifery http://wacebnm.curtin.edu.au	Web page reviewed: Resources – 'Reports, Guidelines and Article'
Other Accident Commissions	

Motor Accidents Authority NSW www.maa.nsw.gov.au/	Web page reviewed: Publications & Reports – MAA Guidelines – Guides for Professionals
Accident Compensation Corporation www.acc.co.nz/index.htm	Web page reviewed:: For Providers – Clinical Best Practice – Published Clinical Guidelines
WorkSafe VIC www.workcover.vic.gov.au	Web page reviewed: Safety & Prevention; Health and Safety Topics
Work Cover NSW www.workcover.nsw.gov.au	Web page reviewed: Publications
Work Cover WA www.workcover.wa.gov.au	Web page reviewed: Publications – Publications for health providers