

Hypnosedatives for anxiety, insomnia and muscle spasm

Evidence Map

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EXECUTIVE SUMMARY

The aim of this work is to provide an evidence map of the existing high level studies (systematic reviews and evidence-based guidelines) on the benefits and harms of hypnotosedatives for anxiety, insomnia and muscle spasm.

The drugs included under the title of ‘hypnotosedatives’ were:

- benzodiazepines: alprazolam, bromazepam, clobazam, diazepam, flunitrazepam, lorazepam, midazolam, nitrazepam, oxazepam, temazepam, triazolam
- non-benzodiazepine hypnotics: zolpidem, zopiclone

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]).

The numbers of studies identified for each indication were as follows:

Anxiety: 18 SRs, 5 EBGs

Insomnia: 17 SRs, 2 EBGs

Muscle Spasm: 1 SR, 0 EBGs

One SR was about the use of hypnotosedatives for all three indications. All other EBGs and SRs were about one indication only.

BACKGROUND

Sedatives are a class of psychoactive drugs commonly prescribed as treatment for sleep disorders, anxiety and a variety of related conditions. In order to develop and update policies for their use in patients with these conditions, the Health Services Group of the Transport Accident Commission and WorkSafe Victoria (TAC/WSV) requested a map of the available high level evidence examining the benefits and harms of the use of sedatives in anxiety, insomnia and muscle spasm.

The term ‘hypnosedatives’ refers to benzodiazepines, benzodiazepine derivatives, and a group of non-benzodiazepine hypnotic drugs (referred to as “Z-drugs”), that includes zolpidem and zopiclone.

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 available. Their range of action – sedative/hypnotic, anxiolytic, anticonvulsant and muscle relaxant – combined with low toxicity and cost gained them popularity among physicians and patients.(1)

The “Z-drugs” are hypnotics with similar pharmacology to benzodiazepines. They have been promoted as being safer than benzodiazepines and in many countries they are the most widely prescribed drugs for insomnia.(2)

Since the early 1980’s studies have regularly pointed out the risks and adverse effects related to long term use of benzodiazepines and other hypnotics.(3) The aim of this work is to provide an evidence map of the existing high level studies (systematic reviews and evidence-based guidelines) on the benefits and harms of hypnosedatives for anxiety, insomnia and muscle spasm.

THE QUESTION

The research questions initially posed were:

- In what conditions are sedatives (benzodiazepine and non-benzodiazepine) indicated?
- What is the effectiveness of sedatives in these conditions?
- What is the effect of sedatives on function, quality of life, return to work, other medication use?
- In what conditions/patient types should sedatives not be used, used short term only or used with caution?
- What risks are associated with the use of sedatives?

There is no well defined, universally accepted definition of what a sedative is, nor a definitive list of drugs that are considered sedatives. Drugs that people might refer to as ‘sedatives’ can fall under many different drug classes such as ‘sedatives’, ‘hypnotics’, ‘anti-anxiety agents’, or ‘complementary medicines’, depending on the organization classifying the drugs. Such a broad list of drugs, combined with open scope on conditions for which they are indicated meant that the research questions initially posed would be unfeasible.

After further discussion, the scope of the question was narrowed from ‘sedatives’ to ‘hypnosedatives’, which comprises benzodiazepines and selected non-benzodiazepine hypnotic agents. The drugs chosen were the

benzodiazepines listed in MIMS as either ‘anti-anxiety agents’ or ‘sedatives, hypnotics’, and two non-benzodiazepine hypnotics: zolpidem and zopiclone (see Table 1).

The question was further refined to include three specific indications:

- What is the effectiveness of hypnotosedatives in anxiety?
- What is the effectiveness of hypnotosedatives in insomnia?
- What is the effectiveness of hypnotosedatives in muscle spasm?
- What are the risks associated with hypnotosedative use in these conditions?

Table 1. List of included hypnotosedatives

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

METHODS

The Search

Searches of Medline and Embase, and the internet were conducted to identify systematic reviews and evidence based clinical practice guidelines (see Appendix 1 for further detail).

Inclusion and exclusion criteria

Search results were screened by two reviewers according to predetermined inclusion and exclusion criteria (see Appendix 1).

For a study to be included, at least one of the hypnotosedatives 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

For included studies, the following data was extracted

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

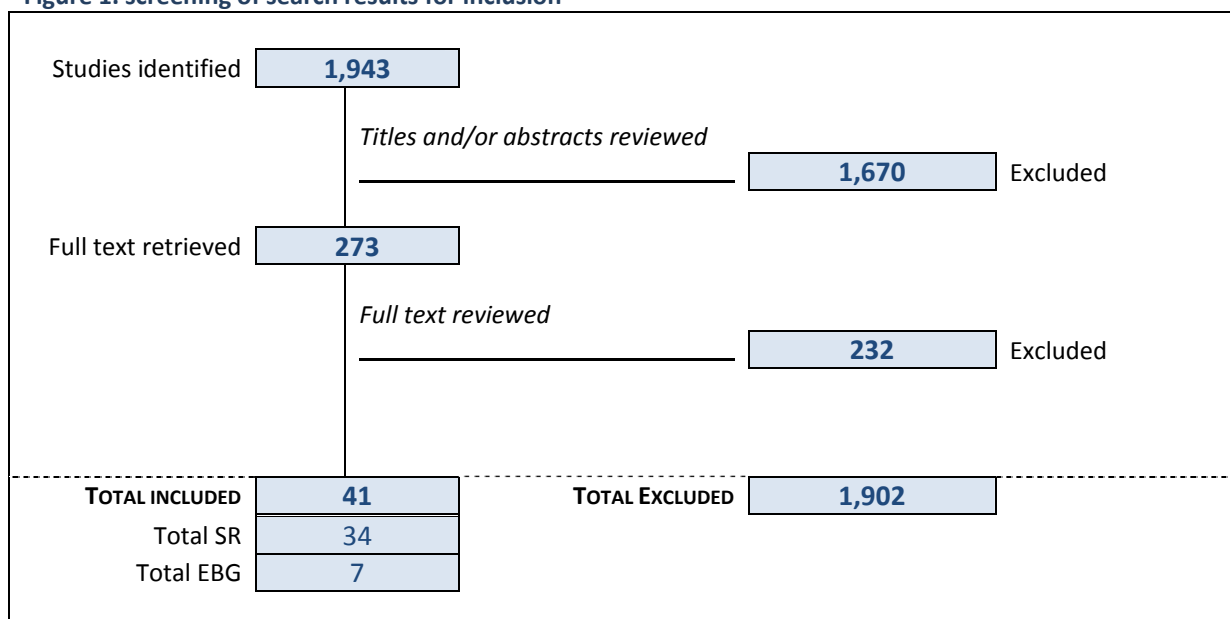
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The extracted data was tabulated in evidence maps to allow determination of the volume of existing evidence, and identify the gaps.

RESULTS

The search returned 1,943 results. After screening, a total of 41 relevant references were identified, which included 34 Systematic Reviews (SRs) and 7 evidence-based guidelines (EBGs) (see Figure 1).

Figure 1. screening of search results for inclusion



There were 18 SRs and 5 EBGs on hypnotosedatives for anxiety; 17 SRs and 2 EBGs for insomnia; and 1 SR for muscle spasm. There were no EBGs on hypnotosedatives for muscle spasm (Table 2). One of the studies was a systematic review of hypnotosedatives for all three indications. All other guidelines and systematic reviews were about one indication only.

Table 2. Evidence map for each indication

Indication	Systematic Reviews	Evidence Based Guidelines
Anxiety	18	5
Insomnia	17	2
Muscle spasm	1	0

The number of SRs and EBGs for each drug by indication are presented in Table 3 and more detailed information is included in Tables 4-8. A reference list of included studies is presented in Appendix 2.

Table 3. Evidence map for each drug by indication

DRUG	ANXIETY		INSOMNIA		MUSCLE SPASM		TOTAL*	
	SR	EBG	SR	EBG	SR	EBG	SR	EBG
Benzodiazepines**	14	5	10	1	1	0	23	6
Alprazolam	16	2	2	0	1	0	17	2
Bromazepam	10	1	0	0	0	0	10	1
Clobazam	4	0	0	0	0	0	4	0
Diazepam	11	2	5	1	1	0	15	3
Flunitrazepam	2	0	5	0	0	0	7	0
Lorazepam	8	2	5	0	0	0	13	2
Midazolam	2	0	4	0	0	0	6	0
Nitrazepam	2	0	7	1	0	0	9	1
Oxazepam	4	0	2	0	0	0	6	0
Temazepam	2	0	11	2	0	0	13	2
Triazolam	4	0	10	1	1	0	13	1
Zolpidem	0	0	14	2	0	0	14	2
Zopiclone	1	0	8	1	0	0	9	1

*'total' refers to the total number of SRs or EBGs for each drug, this figure may differ from the sum of the row, as one SR was relevant to all three indications.

**papers that reported results or made recommendations about 'benzodiazepines' as a group

Table 4. Included systematic reviews of hypnosedatives for anxiety

STUDY	Blanco 2003 p427	Blanco 2003 p29	Busto 1998	Cox 1992 p175	Cox 1992 p300	Furukawa 2001	Gould 1997	Hidalgo 2007	Inada 2003	Ipser 2006	Ipser 2008	Kaplan 2005	Mahe 2000	Martin 2007	Mitte 2005	Robinson 2007	Watanabe 2009	Wetherell 2005
INDICATIONS	SAD	SAD	anxiety, insomnia, 'muscle relaxant'	PDA	PDA, OCD, GAD	anxiety associated with major depression	GAD	GAD	anxiety	treatment-resistant anxiety disorders	SAD	anxiety disorders	GAD	GAD	GAD	SAD	panic disorder	geriatric anxiety disorders
OUTCOMES	B & H	B	H	B	B	B & H	B	B	B	B & H	B & H	B & H	B	B	B	B & H	B & H	B
BENZODIAZEPINES																		
Benzodiazepines*	X	X	X			X	X	X		X		X	X	X	X	X	X	X
Alprazolam	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X
Bromazepam	X	X				X	X	X		X	X				X	X	X	
Clobazam							X					X	X				X	
Diazepam			X		X	X	X	X	X			X	X	X	X		X	
Flunitrazepam						X											X	
Lorazepam						X	X	X				X	X	X	X		X	
Midazolam						X											X	
Nitrazepam						X											X	
Oxazepam						X						X					X	X
Temazepam						X											X	
Triazolam			X			X									X		X	
Other Benzos**	X	X				X	X			X	X	X	X		X	X	X	X
NON-BENZODIAZEPINE HYPNOTICS																		
Zolpidem																		
Zopiclone															X			
Other ***							X											X

*papers that referred to 'benzodiazepines' as a group

** Other benzodiazepines included in some of these systematic reviews were: adinazolam, bentazepam, camazepam, chlordiazepoxide, clonazepam, clorazepate, clotiazepam, cloxazolam, estazolam, flurazepam, flutoprazepam, halazepam, ketazolam, loflazepate, lormetazepam, medazepam, metacazepam, mexazolam, nordazepam, prazepam, propazepam, quazepam, tofisopam

*** The other non-benzodiazepine hypnotics included in some of these systematic reviews was: alpidem

KEY:	
INDICATIONS	OUTCOMES
GAD: generalized anxiety disorder	B: benefits
OCD: obsessive compulsive disorder	H: harms
PDA: panic disorder with agoraphobia	B & H: both benefits and harms
SAD: social anxiety disorder	

Table 5. Included evidence-based guidelines of hypnotosedatives for anxiety

SOURCE	AACAP2007	Andrews 2003	Motor Accident Authority of NSW 2003	NICE 2004 Author: McIntosh 2004	GAC endorsed guidelines Author: Swinson 2006
TITLE	Practice Parameter for the Assessment and Treatment of Children and Adolescents With Anxiety Disorders	Australian and New Zealand clinical practice guidelines for the treatment of Panic disorder and agoraphobia	Anxiety following motor vehicle accidents. A Guidelines & technical report	Clinical Guidelines for the Management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder)	Management of Anxiety Disorders
OUTCOMES	Benefits & Harms	Benefits & Harms	Benefits & Harms	Benefits & Harms	Benefits & Harms
BENZODIAZEPINES					
Benzodiazepines*	X	X	X	X	X
Alprazolam		X			X
Bromazepam					X
Clobazam					
Diazepam		X			X
Flunitrazepam					
Lorazepam		X			X
Midazolam					
Nitrazepam					
Oxazepam					
Temazepam					
Triazolam					
Other Benzos**		X			X
NON-BENZODIAZEPINE HYPNOTICS					
Zolpidem					
Zopiclone					

*papers that referred to 'benzodiazepines' as a group

** Other benzodiazepines included in some of these systematic reviews were: adinazolam, and clonazepam

Table 6. Included systematic reviews of hypnotosedatives for insomnia

STUDY	Bain 2006	Buscemi 2007	Busto 1998	Dundar 2004	Glass 2005	Grad 1995	Hajak 2003	Holbrook 2000	Holm 2000	Joya 2009	Krystal 2007	Nowell 1997	Smith 2002	Soldatos 1999	Swainston-Harrison 2005	Van-Liempt 2006	Verster 2006
INDICATIONS	chronic insom	chronic insom	anxiety, insom, muscle spasm	insom	insom	insom	insom	insom	insom	insom	insom	chronic, primary insom	insom	insom	insom	disordered sleep in PTSD	insom
OUTCOMES	B & H	B & H	H	B & H	B & H	B & H	H	B & H	B & H	H	B	B	B	H	B & H	B	H
BENZODIAZEPINES																	
Benzodiazepines*	X	X	X	X	X	X		X				X	X				X
Alprazolam			X									X					
Bromazepam																	
Clobazam																	
Diazepam			X	X		X		X				X					
Flunitrazepam		X			X			X			X						X
Lorazepam		X		X				X				X	X				
Midazolam					X			X					X	X			
Nitrazepam		X		X	X	X		X			X						X
Oxazepam						X											X
Temazepam	X	X		X	X	X		X			X	X	X			X	X
Triazolam	X	X	X		X	X		X			X	X	X	X			
Other Benzos**	X	X		X	X	X		X			X	X	X	X	X	X	X
NON-BENZODIAZEPINE HYPNOTICS																	
Zolpidem	X	X		X	X		X		X	X	X	X	X	X	X	X	X
Zopiclone		X		X	X		X				X		X	X			X
Other ***	X	X		X	X					X	X						

*papers that referred to 'benzodiazepines' as a group

** Other benzodiazepines included in some of these systematic reviews were: chlordiazepoxide, clonazepam, estazolam, flurazepam, loprazolam, lormetazepam, quazepam

*** Other non-benzodiazepine hypnotics included in some of these systematic reviews were: Eszopiclone, zaleplon

KEY:	
INDICATIONS	OUTCOMES
Insom: insomnia	B: benefits
PTSD: post traumatic stress disorder	H: harms
	B & H: both benefits and harms

Table 7. Included evidence based guidelines of hypnotosedatives for insomnia

SOURCE	Bloom2009	NICE 2004
TITLE	Evidence-Based Recommendations for the Assessment and Management of Sleep disorders in older persons	Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia. London: National Institute for Clinical Excellence
OUTCOMES	Benefits & Harms	Benefits & Harms
BENZODIAZEPINES		
Benzodiazepines*		X
Alprazolam		
Bromazepam		
Clobazam		
Diazepam		X
Flunitrazepam		
Lorazepam		
Midazolam		
Nitrazepam		X
Oxazepam		
Temazepam	X	X
Triazolam	X	
Other Benzos**	X	X
NON-BENZODIAZEPINE HYPNOTICS		
Zolpidem	X	X
Zopiclone		X
Other ***	X	X

*papers that referred to 'benzodiazepines' as a group

** Other benzodiazepines included in some of these systematic reviews were: estazolam, flurazepam, lormetazepam, quazepam

*** The other non-benzodiazepine hypnotic included in one guideline was: zaleplon

KEY:	
INDICATIONS	OUTCOMES
Insom: insomnia	B: benefits
PTSD: post traumatic stress disorder	H: harms
	B & H: both benefits and harms

Table 8. Included systematic reviews of hypnotosedatives for muscle spasm

STUDY	Busto 1998
INDICATIONS	anxiety, insomnia, muscle spasm
OUTCOMES	Harms
BENZODIAZEPINES	
Benzodiazepines*	X
Alprazolam	X
Bromazepam	
Clobazam	
Diazepam	X
Flunitrazepam	
Lorazepam	
Midazolam	
Nitrazepam	
Oxazepam	
Temazepam	
Triazolam	X
NON-BENZODIAZEPINE HYPNOTICS	
Zolpidem	
Zopiclone	

*papers that referred to 'benzodiazepines' as a group

DISCUSSION

The benzodiazepines listed in the research question are those licensed for use in Australia and listed in MIMs as either 'anti-anxiety agents' or 'sedatives, hypnotics'. Many studies identified included various other benzodiazepines. Studies from the UK or US often included only those benzodiazepines licensed for use in that country. This should be kept in mind when looking at recommendations or reported results of 'benzodiazepines', as the list of drugs that different authors are referring to are not likely to be the same.

The SRs identified generally focused on the drug/s in question for a particular indication, whereas the EBGs focused on the indication as a whole, including other material such as diagnosis, prevention and non-pharmacological management.

No quality appraisal has been done on any of the included studies.

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.

REFERENCES

1. Ashton H. The diagnosis and management of benzodiazepine dependence. *Current Opinion in Psychiatry*. 2005 May;18(3):249-55.
2. Olson LG. Hypnotic hazards: adverse effects of zolpidem and other z-drugs. *Australian Prescriber*. 2008;31(6):146-9.
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4. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche P, Ioannidis JPA. and the PRISMA Group. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Med*. 2009;6:e1000100.

5. The AGREE Collaboration. The AGREE Instrument. 2010 [updated 2010; cited March 2010]; Available from: www.agreecollaboration.org.

APPENDIX 1: METHODS

TAC/WSV staff assisted in the development of search terms and inclusion exclusion criteria.

Inclusion and exclusion criteria

Inclusion and exclusion criteria were established a priori (Table A1.1) and were applied by two reviewers. Any discrepancies were discussed and resolved.

Table A1.1. Inclusion and exclusion criteria

Patient/ population	<p>Inclusion: patients with:</p> <ul style="list-style-type: none"> • Anxiety (including anxiety disorders) • Insomnia, or • Muscle spasm <p>All ages</p>
	<p>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.</p>
Intervention/ indicator	<p>Inclusion: Studies where the focus is at least one of the following hypnosedatives:</p> <p><u>Benzodiazepines</u></p> <p>Alprazolam Bromazepam Clobazam Diazepam Flunitrazepam Lorazepam Midazolam Nitrazepam Oxazepam Temazepam Triazolam</p> <p><u>Non-benzodiazepine Hypnotics</u></p> <p>Zolpidem Zopiclone</p>
	<p>Exclusion: Studies where the included hypnosedatives were only reported on as a comparator</p>
Comparison/ control	<p>Inclusion: Any</p>
	<p>Exclusion: Nil</p>
Outcomes	<p>Inclusion: Outcomes related to resolution or reduction of problem being treated. Outcomes</p>

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	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: <ul style="list-style-type: none"> • 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 hypnotics 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.

Reviews were considered systematic reviews if they met items 4 and 8 on the PRISMA checklist(4), which involves: a statement of the objectives of the review and the types of studies that will be included, and the search strategy in sufficient detail that it could be repeated.

Guidelines were considered to be Evidence-Based Guidelines if they met AGREE(5) criteria 8 and 12, which involves: the search strategy in sufficient detail that it could be repeated, and an explicit link between recommendations and the supporting evidence.

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 A1.2. Databases accessed

Database name	Dates covered	Date searched	Refs
Embase	1980 to 2010 Week 04	05/02/2010	1,444

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Medline	1950 to January Week 3 2010	05/02/2010	595
TOTAL			1,921

Table A1.3. Search strategies used

Database name	Strategy
Embase	<p>ES_Sedatives_Embase_with SR etc filter</p> <ol style="list-style-type: none"> 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. (Ale pam 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.

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	<p>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</p>
Medline	<p>ES_Sedatives_Medline_with SR etc filter</p> <p>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</p>

<p>32. Nitrazepam/ 33. (Alodorm or Mogadon).ti,ab. 34. or/32-33 35. Oxazepam/ 36. (Alepan 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</p>
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Guideline searches

Many clinical practice guidelines are published as ‘stand alone’ documents on the internet, rather than as articles in peer-reviewed journals. Additional search methods are needed to identify guidelines published outside the health literature. Guidelines can be found by searching the internet as a whole, searching relevant websites, and searching electronic health databases.

An evidence-based guideline is different to a systematic review in that a systematic review usually attempts to answer one clinical question, whereas a guideline may encompass many clinical questions, and the corresponding systematic reviews.

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.

Internet searches to identify relevant evidence-based guidelines and systematic reviews

The systematic search methodology would normally include a strategy with relevant terms in the Google ‘Advanced Search’ function. However, the Google advanced search screen did not have the capacity to allow a search which encompassed all the possible names due to the size and complexity of the topic (13 drugs for 3 indications). Sample tests with abbreviated name options did not suggest that any possible yield would repay the time spent in attempting the numerous searches that would be required.

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Table A1.4. Websites searched to identify relevant guidelines

Guideline Services		
<p>National Institute of Clinical Studies. Clinical Practice Guidelines Portal</p> <p>http://www.clinicalguidelines.gov.au/</p>	<p>Therapeutic guidelines psychotropic version 6 (2008)</p> <p>http://www.clinicalguidelines.gov.au/browse.php?treePath=F.D001520.D004644.D001007&pageType=2&fldgIrlD=466&</p> <p>Therapeutic guidelines Respiratory version 4 (2009)</p> <p>http://www.clinicalguidelines.gov.au/search.php?pageType=2&fldgIrlD=1600&</p> <p>My hands shake: Classification and treatment of tremor</p> <p>http://www.racgp.org.au/afp/200909/200909sirisena.pdf</p>	<p>Web page reviewed: Guideline Portal, Browse by condition</p>
<p>National Health and Medical Research Council (NHMRC) www.nhmrc.gov.au</p>	<p>Australian Guidelines for the Treatment of Adults with Acute Stress Disorder and Posttraumatic Stress Disorder</p> <p>http://www.nhmrc.gov.au/publications/synopses/mh13syn.htm</p>	<p>Web page reviewed: Guidelines, health</p>
<p>National Institute for Health and Clinical Excellence UK (NICE) www.nice.org.uk</p>	<p>Anxiety: management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care.</p> <p>http://guidance.nice.org.uk/CG22</p> <p>Insomnia - newer hypnotic drugs: Zaleplon, zolpidem and</p>	<p>Web page reviewed: Our guidance, health topic, Mental health and behavioural conditions</p> <p>Web page reviewed: Our guidance, health topic, Musculoskeletal</p>

	zopiclone for the management of insomnia http://guidance.nice.org.uk/TA77	
New Zealand Guideline Group (NZGG) www.nzgg.org.nz	Identification of Common Mental Disorders and Management of Depression in Primary Care http://www.nzgg.org.nz/guidelines/dsp_guideline_popup.cfm?guidelineCatID=8&guidelineID=152	Web page reviewed: Guidelines and Reports
Scottish Intercollegiate Guidelines Network (SIGN) www.sign.ac.uk	Early management of patients with a head injury http://www.sign.ac.uk/guidelines/fulltext/110/index.html	Web page reviewed: Guidelines Mental Health Web page reviewed: Guidelines Other
Guidelines International Network www.g-i-n.net	Australian guidelines for the treatment of adults with acute stress disorder and posttraumatic stress disorder (MH 13) http://www.g-i-n.net/membership/members/nhmrc-au-national-health-and-medical-research/guidelines/australian-guidelines-for-the-treatment-of-adults Effectiveness of nasal continuous positive airway pressure (nCPAP) in obstructive sleep apnoea in adults (HPR 21, HPR 22) http://www.g-i-n.net/membership/members/nhmrc-au-national-health-and-medical-research/guidelines/effectiveness-of-nasal-continuous-positive-airway	Web page reviewed:: International Guideline Library (members only) 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	Anxiety http://www.gacguidelines.ca/index.cfm?ACT=topics&Summary_ID=233&Topic_ID=24	Web page reviewed: List all topics and summaries

<p>National Guideline Clearinghouse US (NGC)</p> <p>(1) searched on 07/02/10 – 13 Results total</p> <p>www.guidelines.gov</p>	<p>Guidelines for the management of severe traumatic brain injury. Anesthetics, analgesics, and sedatives.</p> <p>http://www.guidelines.gov/summary/summary.aspx?doc_id=10999&nbr=005779&string=%28Alprazolam+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%29</p> <p>Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia.</p> <p>http://www.guidelines.gov/summary/summary.aspx?doc_id=8641&nbr=004814&string=%28Alprazolam+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%29</p>	<p>Searched by:</p> <p>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)</p> <p>Disease/Condition: (trauma OR spinal OR spine OR brain OR anxiety OR sleep OR insomnia OR muscle OR muscular))</p>
<p>TRIP Database</p> <p>(1) searched on 07/02/10 – 1,780 Results total</p> <p>Evidence Based Synopses 81</p> <p>Systematic Reviews 114</p> <p>Guidelines:</p> <p>Aus. & NZ 12</p> <p>Canada 5</p>	<p>Adult Conditioned Insomnia: Diagnosis to Management (CPD access)</p> <p>Recommendations for the Safe Transfer of Patients with Brain Injury 2006</p> <p>http://www.aagbi.org/publications/guidelines/docs/brain_injury.pdf</p> <p>Evidence-based treatment for the pharmacological treatment of anxiety disorders National Library of Guidelines (UK) 2006 (CPD access)</p>	<p>Searched by:</p> <p>Drug names</p>

UK 58 USA 8 Other 4 www.tripdatabase.com	Implementing and ensuring Safe Sedation Practice for healthcare procedures in adults. Report of an Intercollegiate Working Party chaired by the Royal College of Anaesthetists http://www.rcoa.ac.uk/docs/safesedationpractice.pdf	
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/	http://www.maa.nsw.gov.au/default.aspx?MenuID=170 MAAS Guidelines <u>MAS Guidelines</u> <ul style="list-style-type: none"> • Medical Assessment Guidelines - 1 October 2008 📎 (2.1mb) • Medical Assessment Guidelines May 2006 📎 (77kb) (MS Word version 📎 929kb) 	Web page reviewed: Publications & Reports – MAA Guidelines – Guides for Professionals

	<p><u>CARS Guidelines</u></p> <ul style="list-style-type: none"> • Claims Assessment Guidelines - 1 October 2008 (Amended October 1 2009) 📎 (260kb) • Claims Assessment Guidelines May 2006 📎 (77kb) (MS Word version 📎 929kb) <hr/> <p>Injury Management Guidelines</p> <ul style="list-style-type: none"> • Guides for professionals • Guides for injured people 	
<p>Accident Compensation Corporation www.acc.co.nz/index.htm</p>	<p>Treatment profiles http://www.acc.co.nz/for-providers/clinical-best-practice/PRV00053</p>	<p>Web page reviewed:: For Providers – Clinical Best Practice – Published Clinical Guidelines</p>
<p>WorkSafe VIC www.workcover.vic.gov.au</p>	-	<p>Web page reviewed: Safety & Prevention; Health and Safety Topics</p>
<p>Work Cover NSW www.workcover.nsw.gov.au</p>	-	<p>Web page reviewed: Publications</p>
<p>Work Cover WA www.workcover.wa.gov.au</p>	-	<p>Web page reviewed: Publications – Publications for health providers</p>

APPENDIX 2: INCLUDED STUDIES

List of included systematic reviews

1. Bain KT. Management of chronic insomnia in elderly persons. *American Journal Geriatric Pharmacotherapy*. 2006 Jun;4(2):168-92.
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List of included evidence-based guidelines

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