Guide to Using Psychotropic Medication to Manage Behaviour Problems among Adults with Intellectual Disability

Technical Document

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Technical Document Section 3.5: Systematic Reviews: Antianxiety, Benzodiazepines and Beta-blockers

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Anti-anxiety, Benzodiazepines and Beta-blockers

Identification of primary trials on the use of anti-anxiety medication, benzodiazepines and beta-blockers in the management of behaviour problems in adults with a learning disability.

Databases used

	Search 1	Search 2	Search 3
PsycInfo	1990 to week 2 Oct 2005	1872 to 1990	1990 to week 3 June 2005
Medline	1990 to week 1 Oct 2005	1966 to 1990	1990 to week 4 June 2005
Embase	1990 to 43rd week of 2005	1980 to 1990	1990 to 26th week of 2005
Cinahl	1990 to week 2 Oct 2005	1982 to 1990	1990 to week 3 June 2005

Search terms

The databases were searched using the 84 phrases mentioned earlier, with the addition of the following search terms adapted specifically for the anti-anxiety medication review:

85. exp benzodiazepines/
86. exp sedatives/
87. exp adrenergic blocking drugs/
88. (clobazam or clonazepam or midazolam or hypnovel or nitrazepam or flunitrazepam or rohypnol or flurazepam or dalmane or loprazolam or lormetazepam or temazepam or zaleplon or sonata or zolpidem or stilnoct or zopiclone or zimovane or diazepam or alprazolam or xanax or chlordiazepoxide or clorazepate or tranxene or lorazepam or oxazepam).tw.
89. (buspirone or buspar).tw.
90. melatonin.tw.
91. (propranolol or inderal or acebutolol or secadrex or atenolol or tenormin or bisoprolol or cardicor or emcor or monocor or carvedilol or celiprolol or esmolol or labetalol or metoprolol or nadolol or corgard or Nebivolol or Oxprenolol or trasicor or pindolol or visken or sotalol or timolol).tw.
92. exp BUSPIRONE/
93. exp MELATONIN/
94. or/84-93
95. 84 and 94
96. limit 95 to (human and "300 adulthood <age 18 yrs and older>" and human and yr=1990-2005)

For search 2:
In order to perform this search, the limits of search 1 were reset so that all articles available in the databases, dated before 1990, could be retrieved. No new search terms were added to the original search.

For search 3:
In order to perform this search, the limits of search 1 were reset so that all articles related to children/ adolescents (under the age of 18 years) could be retrieved. No new search terms were added to the original search.

Results

Each of the databases retrieved the following number of citations for the different searches:

Database	Search 1	Search 2	Search 3
PsycInfo	97	24	27
Medline	140	57	69
Embase	483	18	60
Cinahl	222	18	70

Selection process

For search 1:
942 citations altogether were generated by the searches. Of these, 891 were eliminated on the basis of duplication, title and abstract. The remaining 51 citations were scrutinised by applying the inclusion/ exclusion criteria, which resulted in a further 32 being excluded. At this stage, there were 19 citations left over, of which 11 were kept in aside in a box due to small sample size, 7 full texts were required and 1 citation for which there was no abstract available. This 1 latter citation was submitted to the GDG members for scrutiny and a consensus was reached to exclude it. Hand searching did not reveal any new studies, it was necessary to obtain the full text for 1 but this did not fulfil the inclusion criteria, the reason for excluding this study can be found in table 10.

A breakdown of the selection process for this search is shown in figure 13.

For search 2:
This search produced 117 citations altogether including case series to controlled trials. All citations were scanned to ensure that any relevant controlled trials would not be missed. However, all citations were excluded on the basis of duplication, title and abstract.

A breakdown of the selection process for this search is shown in figure 14.

For search 3:
A total of 226 citations were produced altogether including case series to controlled trials. All citations were scanned to make sure that any relevant controlled trials would not be missed. No citations were found to be appropriate for inclusion and all were excluded based on duplication, title and abstract.

A breakdown of the selection process for this search is shown in figure 15.

Results: Included studies

Search 1:
The full texts of 7 citations were examined and 6 failed to merit inclusion, the reasons for which are also given in table 1.4. Therefore, only 1 study was included from this review and data extraction and quality assessment was completed for this. The suitable study comprised of a prospective open trial on buspirone (King *et al*, 1996). The characteristics of this study are given in table 11.

Search 2 and 3 yielded no additional studies.

An overall summary of the findings of this review is shown in figure 16.

Figure 13: Search 1 – Anxiolytics/ beta-blockers

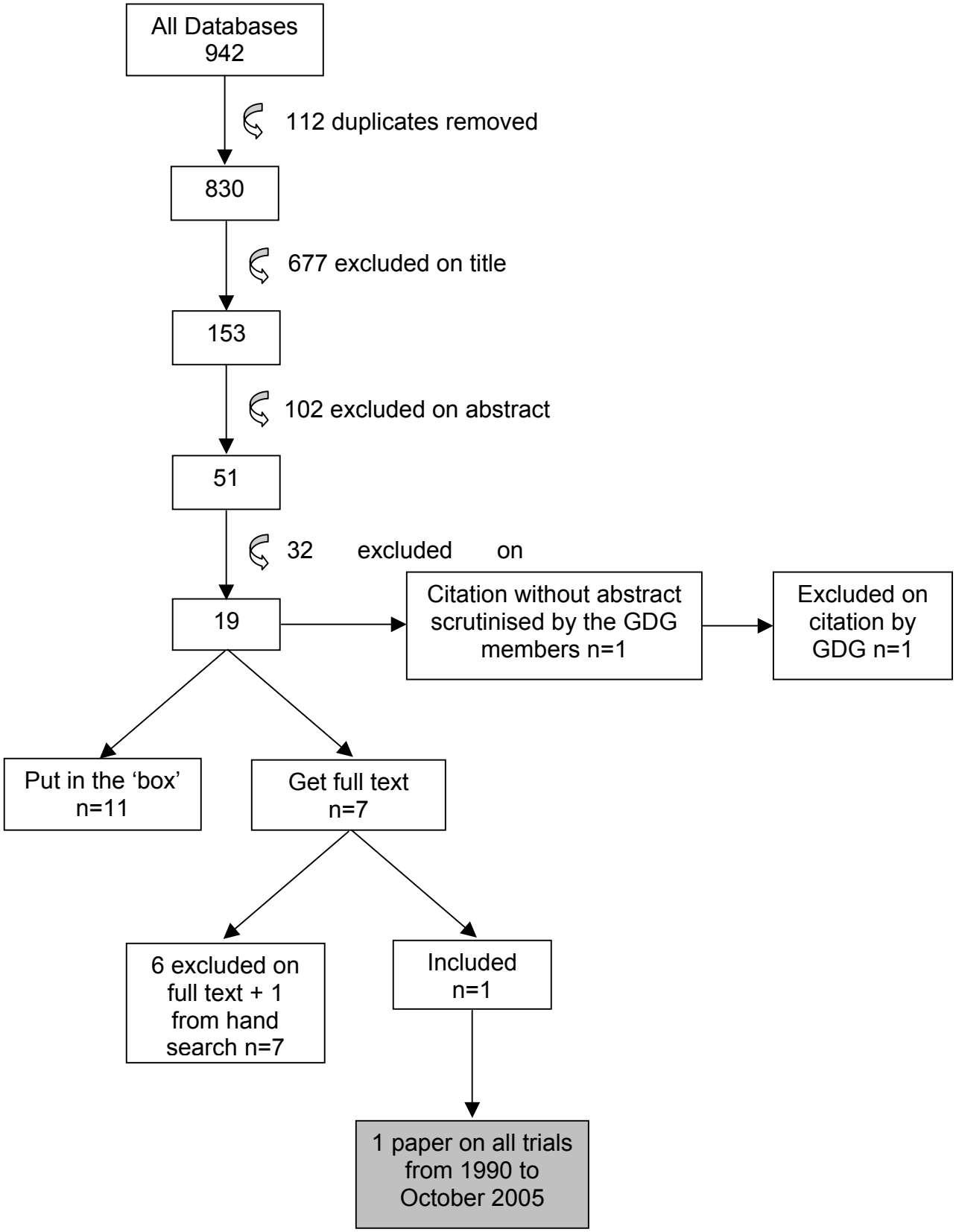


Figure 14: Search 2 - Anxiolytics/ beta-blockers

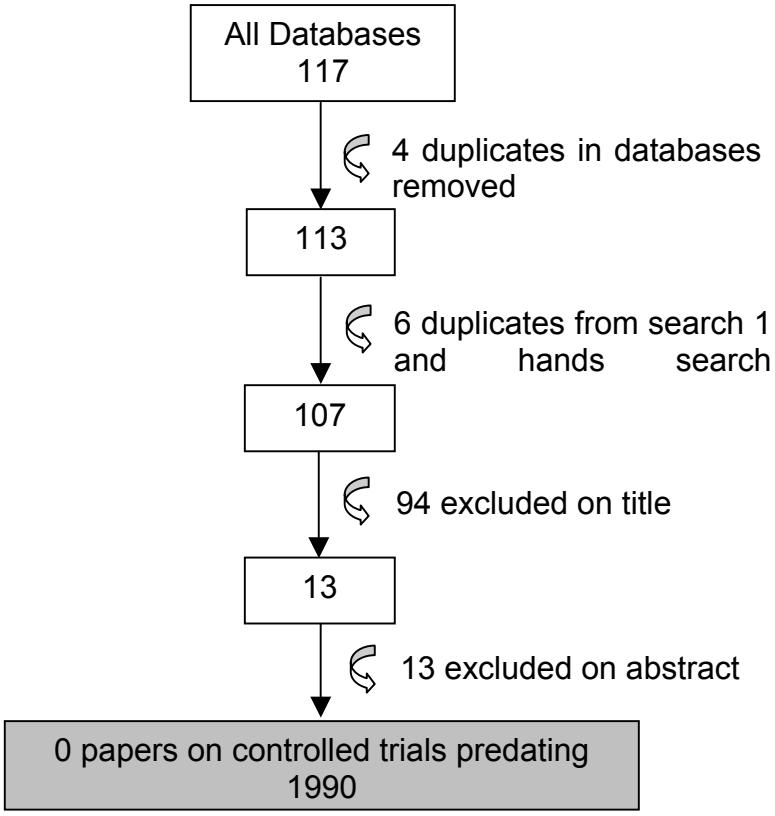


Figure 15: Search 3 - Anxiolytics/ beta-blockers

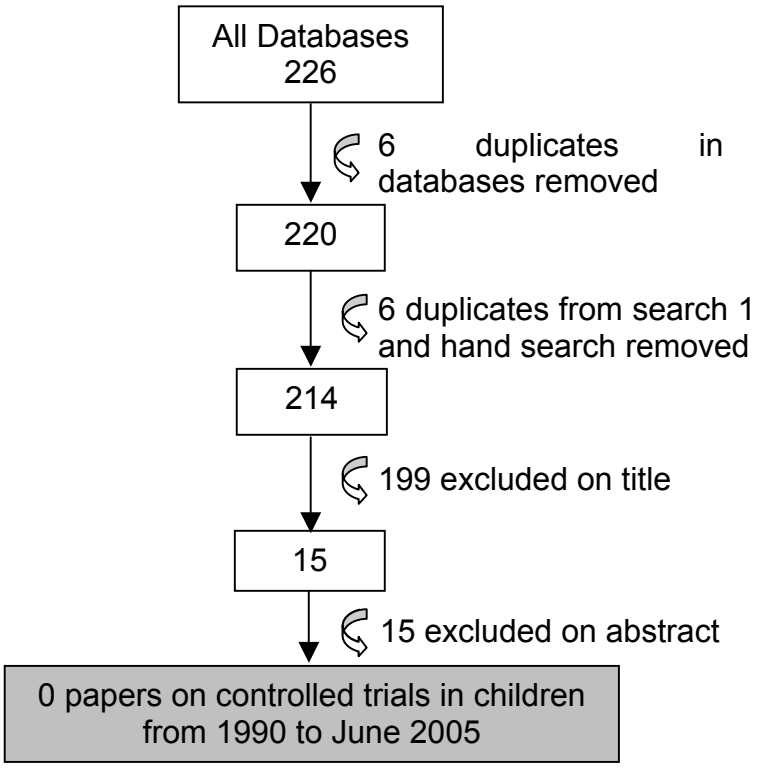
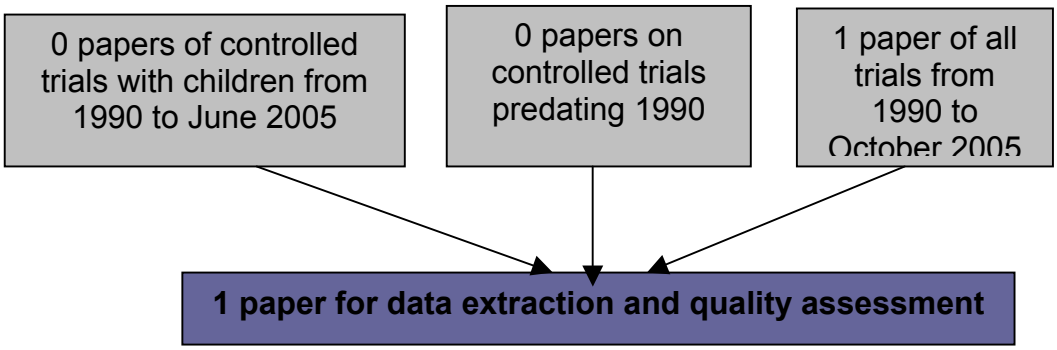


Figure 16: Summary of Anxiolytics/ Beta-blockers search



Anxiolytics/ beta-blockers Review: Summaries of included studies

Prospective study

King et al. (1996)

Participants
26 adults, age range 25-63 (46% male). 21 (81%) had a profound LD, 4 (15%) severe and 1 (4%) moderate. All presented with aggression and/ or self injurious behaviour.

Intervention
Buspirone (starting dose not specified) given at a maximum dose of 25-60mg/ day (average dose 52mg/ day), no wash-out period and other medications were allowed. The average length of time on treatment was 170 days (range 28-310 days).

Method
Prospective, uncontrolled, open trial.

Follow-up
Participants were assessed daily by staff members and daily records were kept for at least 3 months.

Outcomes
1. The number of episodes (frequency) of target behaviour were recorded using an in house data recording system. 2. The severity of SIB and aggression was rated using a 5-point scale (1=no occurrence of behaviour to 5=life threatening).

Results
For SIB frequency, there were no significant differences between pre- and post treatment values. In terms of aggression frequency, those with autism deteriorated and those without improved ($p=0.003$). The severity ratings showed a differing response within categories for aggression but overall those with autism did not respond at all. There was no difference for SIB.

Comments
This study has struggled to find any benefits from buspirone. There was no intention to treat analysis, the exclusion criteria was not clear and the outcome assessments lacked validity. Furthermore, the results have been rather complicatedly presented using a number of scatter graphs. This study scored 3/9 on quality assessment.

Table 10: Studies excluded on full text

Study	Summary	Reason for exclusion
De Marinis, 1990	This was a prospective open trial involving the acute administration of 5 different substances in 10 adults with a LD displaying stereotypy. Diazepam was one of the medications and given as a single dose IM. This reduced the frequency of stereotypic movements.	This was the only study considering IM treatment and therefore, excluded. Furthermore, the results from this study were not directly related to anxiolytics.
Ishizaki, 1999	An open trial of melatonin administered for sleep and emotional/ behavioural problems in a sample of which 20 had a LD. Melatonin did not have any effect on stereotypical behaviour. There was a greater impact on the sleep disorders.	This study included both adults and children with no separate results for those aged 18 years or over.
Perez, 1997	This was a RCT investigating the effects of a combination of pindolol and fluoxetine on major depression. This combination was more effective than fluoxetine therapy alone.	The population did not have a LD.
Ratey, 1992	This was a RCT exploring the effectiveness of nadolol for the treatment of aggression in chronic psychiatric patients. The frequency of aggression significantly decreased in those treated with nadolol compared with placebo.	There were 5 participants with a LD but no separate results for these.
Rossi, 1999	This was an open trial of niaprazine in autistic participants presenting with severe mood disorders, aggressiveness and hyperkinesia. The medication was more effective in participants with a mild or moderate LD.	This study included both adults and children with no separate results for those aged 18 years or over.
Silver, 1999	This was an open phase study followed by an add-on double blind, medication withdrawal phase. 7/10 participants had a greater than 50% improvement in aggressive behaviour after the first phase of the study.	There were 6 participants with a LD but no separate results for these.
Tsiouris, 2003	This was an open trial assessing whether psychotropic medication treatment of a previously undiagnosed psychiatric disorder would reduce the incidence of SIB. It was suggested that SIB in LD that is resistant to behaviour modification and environmental changes, could be effectively managed by treatment of the underlying psychiatric disorders with appropriate psychotropics.	There is no single intervention included in the study. The intervention was the diagnosis of an underlying psychiatric disorder and then this was treated appropriately.

Table 11: Studies included in the anxiolytics and beta-blockers review

Author/ **Evidence category (EC)**	**Medication/ Average daily dose**	**Target behaviour**	**Type of study**	**N**	**Outcome measures**	**Results**
King 1996 EC III	Buspirone 52mg	Aggression, SIB	Prospective Uncontrolled	26	Frequency counts, 5-point severity rating scale	There were no significant differences between pre and post treatment.

Evidence Category - III: non-experimental study such as case series

References for search 1

Anxiolytics/ Benzodiazepines/ Beta-blockers Review

Included studies (N≥10)

1. King BH & Davanzo P. Buspirone treatment of aggression and self-injury in autistic and nonautistic persons with severe mental retardation. *Developmental Brain Dysfunction* 1996; 90 (1): 22-31.

Anxiolytics/ Benzodiazepines/ Beta-blockers Review

Relevant studies (N<10)

1. Calamari JE, McNally RJ, Benson DS & Babington CM. Case study: Use of propranolol to reduce aggressive behavior in a woman who is mentally retarded. *Behavioral Residential Treatment* 1990; 5 (4): 287-296.
2. Cohen IL, Tsiouris JA & Pfadt A. Effects of long-acting propranolol on agonistic and stereotyped behaviors in a man with pervasive developmental disorder and fragile X syndrome: A double-blind, placebo-controlled study. *Journal of Clinical Psychopharmacology* 1991; 11 (6): 398-9.
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4. Hillbrand M & Scott K. The use of buspirone with aggressive behavior. *Journal of Autism & Developmental Disorders* 1995; 25 (6): 663-664.
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6. Raitasuo S, Rautaoja T & Saarijaervi S. Buspirone treatment in mentally retarded patients with communication difficulties. *Nordic Journal of Psychiatry* 1997; 51 (2): 135-136.
7. Ratey J, Sovner R, Parks A & Rogentine K. Buspirone treatment of aggression and anxiety in mentally retarded patients: A multiple-baseline, placebo lead-in study. *Journal of Clinical Psychiatry* 1991; 52 (4): 159-162.
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11. Verhoeven WMA & Tuinier S. The effect of buspirone on challenging behaviour in mentally retarded patients: An open prospective multiple-case study. *Journal of Intellectual Disability Research* 1996; 40 (6): 502-508.

Anxiolytics/ Benzodiazepines/ Beta-blockers Review

Excluded studies

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2. Bailey DS & Praderio NH. Propranolol. *Journal of Offender Rehabilitation* 1994; 21 (3-4): 223-230.
3. Biswas AB, Finnamore T, Bhaumik S & Collacott R. Skalaphobia - Not to be dismissed. *Mental Health Aspects of Developmental Disabilities* 2001; 4 (3): 119-124.
4. Cadieux RJ. Azapirones: an alternative to benzodiazepines for anxiety. *American Family Physician* 1996; 53 (7): 2349-53.
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6. Connor DF, Ozbayrak KR, Benjamin S, Ma Y & Fletcher KE. A pilot study of nadolol for overt aggression in developmentally delayed individuals. *Journal of the American Academy of Child and Adolescent Psychiatry* 1997; 36 (6): 826-834.
7. De Marinis M, Testa SR, Fiacco F & Agnoli A. Stereotyped movements in mental retardation: A neuropharmacological approach. *New Trends in Clinical Neuropharmacology* 1990; 4 (1): 43-8.
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