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

Technical Document

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

Technical Document Section 3.2: Systematic Reviews: Antipsychotics

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Antipsychotics

Method

Identification of primary trials on the use of antipsychotics 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 3 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 4 June 2005

Search terms

The databases were searched using the 84 phrases mentioned earlier in Section 3.1, with the addition of the following search terms adapted specifically for the antipsychotic medication review:

85. exp neuroleptic agent/
86. neuroleptic drug$.tw.
87. amisulpride$.tw.
88. aripiprazole$.tw.
89. benperidol$.tw.
90. exp chlorpromazine/
91. (chlorpromazine$ or chlorpromasine$).tw.
92. exp clopenthixol/
93. clopenthixol$.tw.
94. exp clozapine/
95. (clozapine$ or clozaril$).tw.
96. exp flupentixol/
97. flupentixol$.tw.
98. exp fluphenazine/
99. fluphenazine$.tw.
100. exp haloperidol/
101. haloperidol$.tw.
102. haldol$.tw.
103. exp loxapine/
104. loxapine$.tw.
105. loxitane$.tw.
106. exp levomepromazine/
107. levomepromazine$.tw.
108. methotrimeprazine$.tw.
109. olanzapine$.tw.
110. zyprexa$.tw.
111. pericyazine$.tw.
112. exp perphenazine/
113. (perphenazine$ or trilafon$).tw.
114. exp pimozide/
115. pimozide$.tw.
116. exp pipotiazine/
117. pipothiazine$.tw.
118. pipotiazine$.tw.
119. exp prochlorperazine/

120. (prochlorperazine$ or compazine$).tw.
121. exp promazine/
122. promazine$.tw.
123. exp promethazine/
124. promethazine$.tw.
125. exp quetiapine/
126. quetiapine$.tw.
127. exp remoxipride/
128. remoxipride$.tw.
129. exp risperidone/
130. (risperidone$ or risperdal$).tw.
131. exp sertindole/
132. sertindole$.tw.
133. exp sulpiride/
134. sulpiride$.tw.
135. exp thioridazine/
136. (mellaril$ or thioridazine$).tw.
137. exp trifluoperazine/
138. (trifluoperazine$ or stelazine$).tw.
139. exp ziprasidone/
140. ziprasidone$.tw.
141. geodon$.tw.
142. exp zotepine/
143. zotepine$.tw.
144. exp clopenthixol/
145. (clopenthixol$ or zuclopenthixol$).tw.
146. exp flupentixol decanoate/
147. depixol$.tw.
148. modecate$.tw.
149. exp haloperidol$/
150. haldol$.tw.
151. risperidal const$.tw.
152. thorazine$.tw.
153. clopixol$.tw.
154. exp zuclopenthixol decanoate/
155. flupenthixol$.tw.
156. risperdal consta$.tw.
157. or/85-156
158. 53 and 84 and 157
159. limit 158 to yr=1990 – 2004

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	187	153	56
Medline	291	87	75
Embase	1067	78	234
Cinahl	371	2	52

Selection process

Search 1:
1916 citations were retrieved using the above databases of which 1796 were excluded based on duplication, title and abstract. This process left 119 citations to which the inclusion/exclusion criterion was applied. In addition to these, various GDG members indicated 5 further citations that were not originally present in the electronic searches giving a total of 124 and these too were subjected to criteria assessment. 67 citations were confidently excluded at this stage and 15 kept in the 'box' as these studies included less than 10 participants. The lack of information available through the other 42 abstracts meant that the full text had to be obtained for these.

Of the 42, 24 were excluded on further inspection, the data for which can be found in table 1. A further 7 studies met the criteria but were boxed due to small sample size and the remaining articles appeared to be relevant and so were assessed in terms of their quality and data extraction was completed. Subsequently, a hand search was conducted which revealed 1 further relevant case study and so this was boxed and 2 studies which were excluded on full text as they failed to adequately meet the inclusion criteria. The data for the 2 latter studies can also be found in table 1.

A breakdown of the selection process is shown in figure 1.

Search 2:
This search produced 320 citations altogether including controlled trials to case series. In order to ensure that no controlled trials would be missed, all these citations were examined. Only 8 articles were eventually deemed to be of interest and so full texts for these were obtained as well as for 11 citations previously discovered through hand searching. All 19 full texts were scrutinised by the inclusion/ exclusion criteria resulting in a further 11 exclusions, the reasons for which are also given in table 1. Quality assessment and data extraction were therefore, carried out for the remaining 6 studies.

A break down of the selection process for this search is shown in figure 2.

Search 3:
This search produced 417 citations altogether including controlled trials to case series. In order to ensure that no controlled trials would be missed, all these citations were examined. Having excluded the majority of these citations based on duplication, title and abstract, there were 5 controlled trials remaining for which the full text was needed in addition to 6 extra citations that had been discovered through hand search at a previous stage. On considering the full text, a further 6 articles were excluded on criteria, the reasons for these are also given in table 1. 5 articles met the inclusion criteria for this search and were subjected to quality assessment and data extraction.

A break down of the selection process for this search is shown in figure 3.

Results: Included studies

Search 1:
In total, 9 studies were found by the searches that fulfilled the inclusion criteria for this review.

Only one RCT was identified (Gagiano *et al*, 2005) which was concerned with the efficacy and safety of the atypical antipsychotic risperidone in the treatment of behaviour problems in adults with a learning disability. There were five prospective case series studies, two of which were related to the effects of risperidone (La Malfa *et al*, 2001; Lott *et al*, 1996), one to do with quetiapine (La Malfa *et al*, 2003) and one associated with the atypical antipsychotic fluphenazine (Gualtieri *et al*, 1990). There was one case crossover study containing both zuclopenthixol and haloperidol (Malt *et al*, 1995). The remaining studies were of a retrospective case series design and consisted of three studies looking into the effects of the atypical antipsychotics clozapine (Boachie *et al*, 1997; Thalayasingam *et al*, 2004) and olanzapine (Janowsky *et al*, 2003).

In addition, two further controlled trials on risperidone (Vanden Borre *et al*, 1993; Zarcone *et al*, 2001) were established for which the population was made up of both children and adults. The results for the adults (aged 18 or over) in these two studies could not be separated but they met all the other eligibility requirements. Therefore, it was decided that these studies would also be included and are presented as controlled trials in both children and adults with ten or more participants.

An overview of the characteristics of these studies is provided in tables 2 and 3.

Search 2:
In all, 6 studies were identified that satisfied the criteria for this search. In 4 of the studies, it was not possible to separate the data for the adults and children, nevertheless, as these included more than ten participants and were randomised controlled trials these too were included.

All studies identified for this search were related to the use of typical antipsychotics. Of those in adults only, one looked at the efficacy of chlorpromazine (Wardell *et al*, 1958) and one of thioridazine (Elie *et al*, 1980).

The studies including both adults and children compared the efficacy of one medication haloperidol with placebo (Aman *et al*, 1989) or explored the effects of two different medications with each other and then compared both the medications in question to placebo. In the latter case, the comparisons made were haloperidol versus thioridazine (Vaisanen *et al*, 1981), sulpiride versus chlorpromazine (Vaisanen *et al*, 1975) and pericyazine versus chlorpromazine (Weir *et al*, 1968).

An overview of the characteristics of these studies is also provided in tables 2 and 3.

Search 3:
5 studies were identified that met all the inclusion criteria. All studies considered the effectiveness of the atypical antipsychotic risperidone in the treatment of behaviour problems in children with a learning disability, in association with other developmental disorders such as autism (Shea *et al*, 2004; Aman *et al*, 2002; The Research Units on Pediatric Psychopharmacology, Autism Network, 2002; Snyder *et al*, 2002; Buitelaar *et al*, 2001).

An overview of the characteristics of these studies is provided in table 4. Figure 4 shows a summary of the findings for the 3 searches.

Figure 1: Search 1 - Antipsychotics

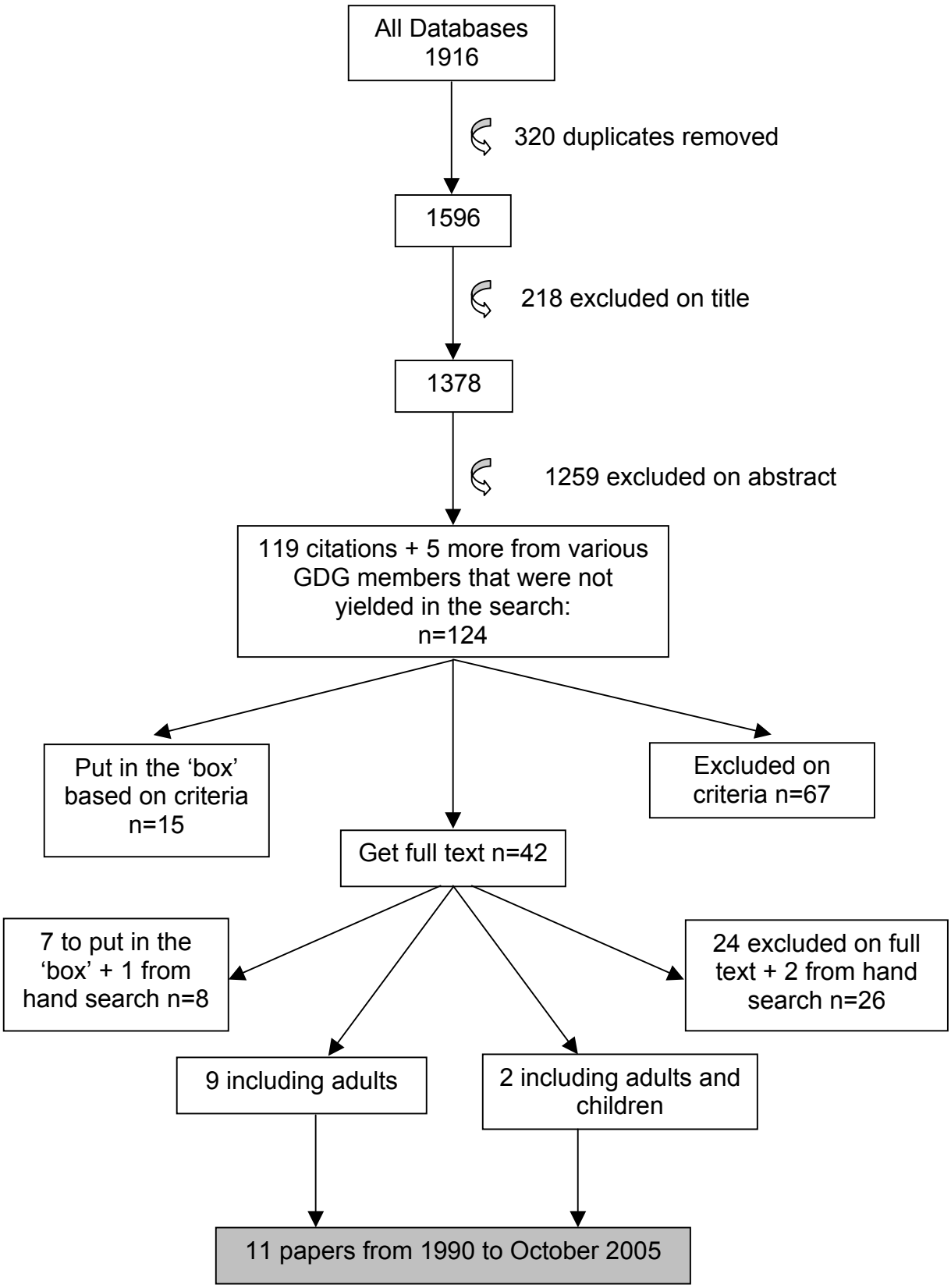


Figure 2: Search 2 - Antipsychotics

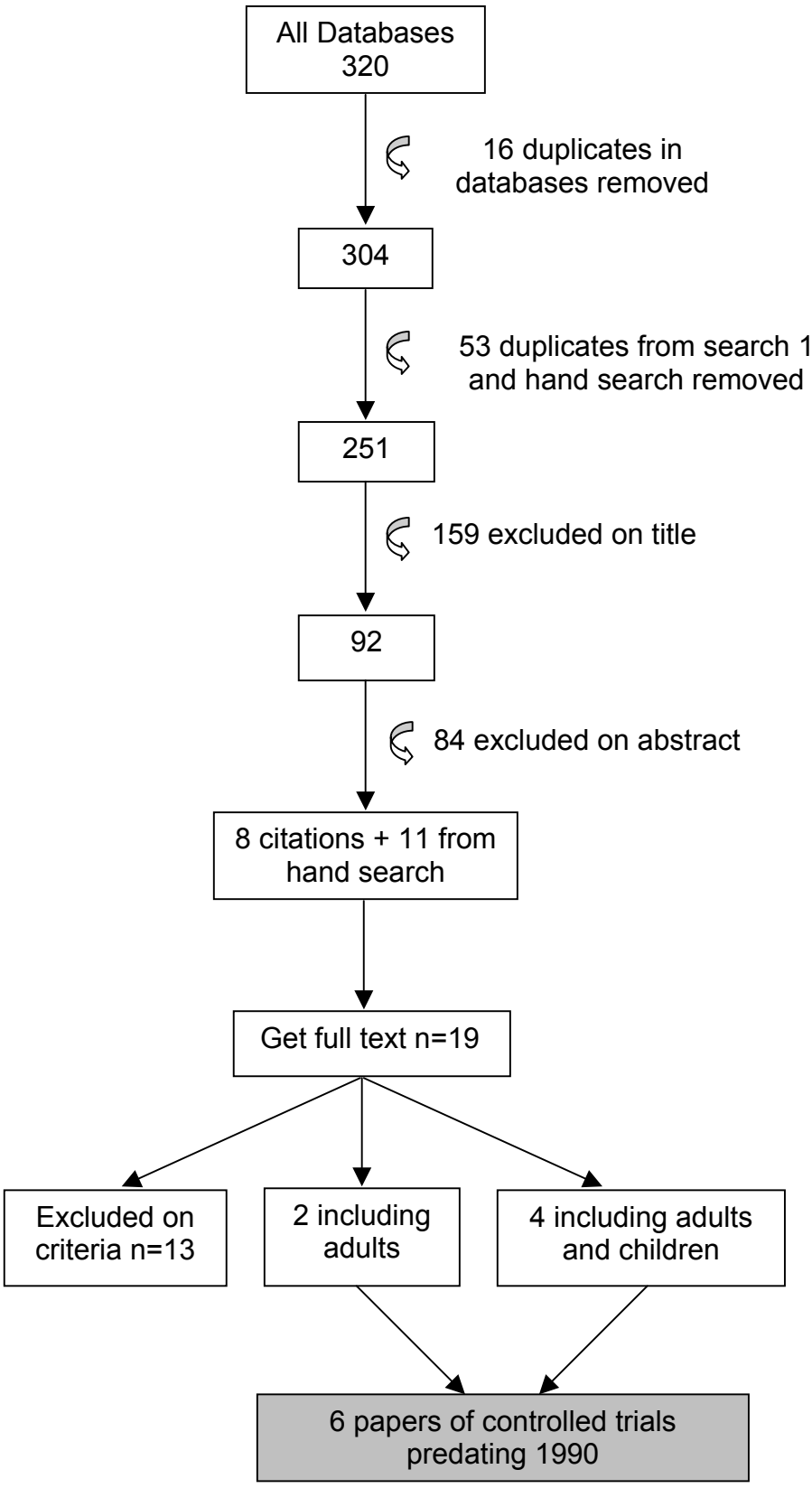


Figure 3: Search 3 - Antipsychotics

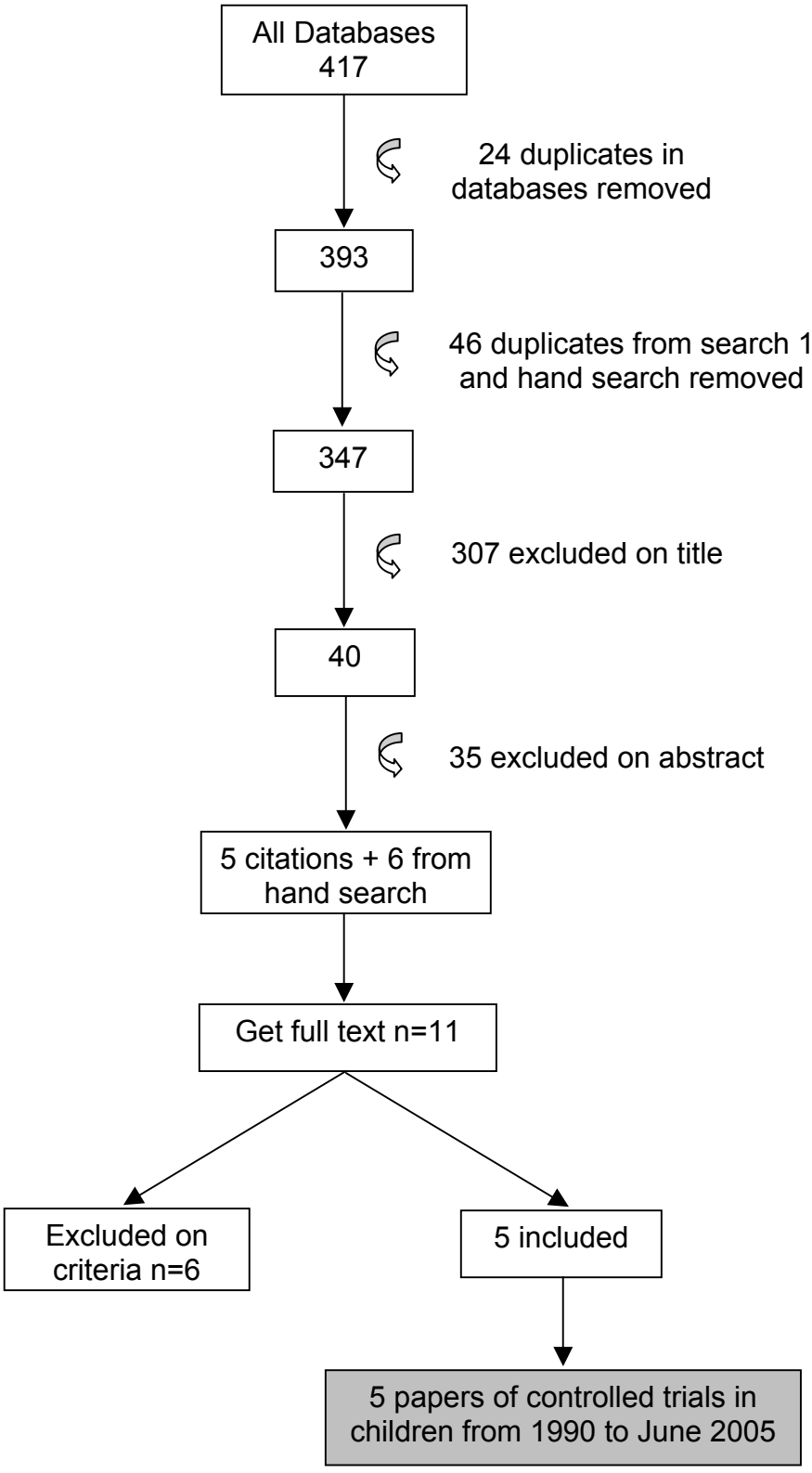
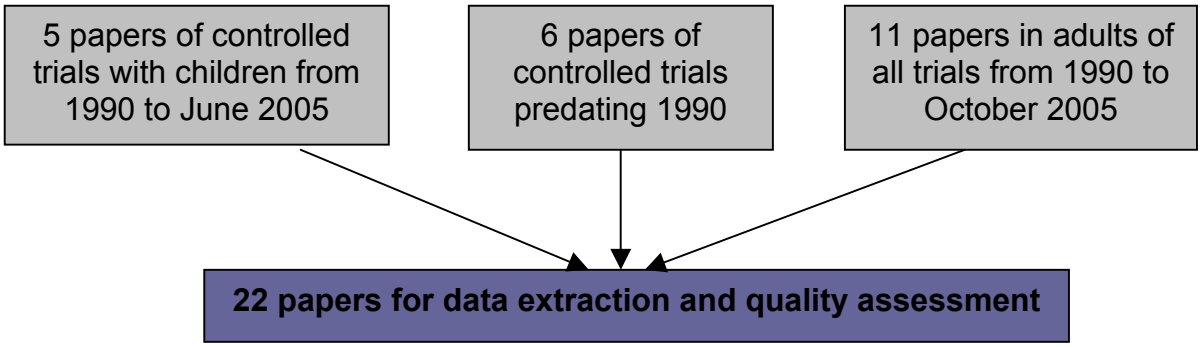


Figure 4: Summary of the antipsychotics search



Antipsychotic Review: Summaries of included studies

Controlled trials

Adults

Gagiano et al. (2005)

Participants
77 adults, study group (n = 39) age range 18-57 years (59% male); control group (n = 38) age range 18-59 years (63% male). Diagnosis of a LD and no psychiatric disorders; DSM-IV Axis I diagnosis of conduct disorder, oppositional defiant disorder, antisocial personality disorder, disruptive behaviour disorder or intermittent disorder. Also Axis II diagnosis of borderline intellectual functioning (16%), mild (55%) and moderate (29%) LD (IQ range 35-84). The target behaviours were various disruptive disorders.

Intervention
Risperidone (n = 39) versus placebo (n = 38) in the RCT phase. Risperidone (n = 58) in open label phase. Dose range 1-4 mg/day (mean 1.8 mg/day) add-on for both trials.

Method
A RCT with a 1-week placebo washout period followed by a 4-week double blind, placebo controlled phase and a subsequent 48-week open label phase. Participants were randomly allocated to treatment groups according to randomisation codes.

Follow-up
Participants were assessed at baseline and then at weeks 2 and 4 for most measures and weekly for extrapyramidal side effects.

Outcomes
1. The Aberrant Behaviour Checklist (ABC), Behaviour Problems Inventory (BPI) and Clinical Global Impressions – Severity scale (CGI-S) were used at baseline and again at 4 weeks for target behaviours.
2. The visual analogue scale (VAS) was rated by a carer.
3. Cognition was assessed using the Continuous Performance Task (CPT) and a modified version of the California Verbal Learning Test – Adult Version (MV-CVLT).
4. Movement disorders were assessed using the Extrapyramidal Symptom Rating Scale (ESRS).
5. A report of adverse events was sought from the participants themselves.

Results
The risperidone group showed greater improvements (as defined by a decrease in ABC scores from baseline) in their total ABC scores at endpoint of the study compared to placebo [-27.3 ± 3.3 points (52.8% improvement) for risperidone versus –14.9 ± 4.0 points (31.3% improvement) for placebo; p=0.036]. The BPI also showed results in favour of risperidone [-0.8 ± 0.4 for risperidone versus –0.2 ± 0.3 for placebo; p<0.05]. Similarly, improvements were noted on the CGI scale whereby after 4 weeks of therapy in each group, the improvement in the risperidone group was 48.5% versus 25% in the placebo group. ESRS scores remained low and decreased slightly by endpoint in both groups. Similar number of patients reported adverse events in both groups – risperidone (R) 23/39 (59%) and placebo (P) 25/38 (66%). Commonly reported effects were somnolence R: 23.1%, P: 15.8%; injury R: 17.9%, P: 13.2%; headache R: 12.8%, P: 7.9%; insomnia R: 10.3%, P: 5.3%; abdominal pain R: 10.3%, P: 0% and aggressive reaction R: 2.6%, P: 10.5%. The median weight of those who received R increased 1.0kg at endpoint, whereas for those on P it remained unchanged.

Comments
Overall, this study achieved a score of 9/14 on quality assessment (4/5 on Jadad criteria). It supports the use of risperidone among adults. There are a reasonable number of participants, good design, good outcome measures reported, and good statistics. However, 4 weeks in the double blind phase is a short period, the study is underpowered, details with regards to the allocation concealment are unclear, the target behaviours are mixed because of the use of the ABC measure and it would have been better if there was just one target behaviour such as aggression.

Malt et al. (1995)

Participants
35 participants (but 1 was withdrawn from endpoint analysis leaving 34), age range 24-59 years (54% male). All had ICD-10 diagnosis of 'mental retardation' and various behavioural problems including SIB and aggression.

Intervention
Zuclopenthixol 2-20 mg/day vs. Haloperidol 0.5-5 mg/day (at the end of the first trial period the average daily dosages were 5.5mg zuclopenthixol and 1.56mg haloperidol; at the end of the second trial period average dosages were 5.13mg zuclopenthixol and 1.23mg haloperidol).

Method
Prospective case crossover design. A single blind, placebo washout period of 2 weeks, followed by a randomised double blind trial of zuclopenthixol or haloperidol for 8 weeks. There was a 2-week, single blind, placebo washout period intervening the crossover phases.

Follow-up
There was a 2-4 week follow-up period for up to a total of 20 weeks.

Outcomes

1. The behaviour subscales of the Schedule for Handicaps Behaviour and Skills (SHBS) consisting of 12 items rated 0 = no problem to 4 = marked problems, with three items on self-injury and stereotyped behaviour added to this.
2. CGI. 3. UKU (Scandinavian scale - Udvalg for Kliniske Undersøgelser) side effect rating scale. Observations were based on interviews with the nursing staff.

Results

The SHBS showed results in favour of zuclopenthixol [reduction in SHBS scores ($p<0.001$)], compared to the reduction in the scores for haloperidol ($p = 0.18$). End-point analysis between the two medications showed zuclopenthixol to be more effective than haloperidol ($p = 0.02$). Analyses at the end of the first medication trial showed reduced mean CGI scores for both zuclopenthixol ($p = 0.04$) and haloperidol ($p = 0.01$) but in the second phase the mean reduction in scores did not reach statistical significance for either. There appeared to be no significant difference between the groups as was revealed on the SHBS in the second phase. The number/ severity of side effects did not differ between the groups.

Comments

The case crossover design has its pros and cons, it is good to avoid problems with matching participants but at the same time may produce confusing results as has happened in the two phases of this study. There is no explanation as to why the results are different in the two phases of the study and there is no analysis done to show whether there is a significant difference between the medications as far as the CGI is concerned. This study scored 7/14 on controlled trials quality assessment.

Elie et al. (1980)

Participants

51 participants, mean age was 32.9 years (65% male). Mean IQ was 32.1 (sd 2.91) for those in the thioridazine group. All participants had a diagnosis of a LD and demonstrated aggressive behaviour that was unmanageable without the use of restraints.

Intervention

Thioridazine 50mg/ daily, given orally or a matching placebo. Treatment duration for both groups was 4 weeks.

Method

Following a 3-week medication washout period where all participants received chlorpromazine, the participants were randomly assigned to receive either thioridazine or placebo. The medications under evaluation were administered in a double blind manner.

Follow-up
The participants were assessed at baseline (after washout) and then weekly during the 4 week experimental phase.

Outcomes
The clinical investigator and nursing staff made outcome assessments. 1. Primary outcome assessing improvement in the severity of aggressive behaviour was the target symptom aggressivity (TSA) scale. 2. Secondary outcome assessing medication efficacy was symptomatic evolution in chief aggressive manifestations (CAM). 3. Tertiary outcome measuring therapeutic value was the CGI scale.

Results
At baseline, the groups did not differ significantly ($p = 0.32$) in mean global score of aggressivity and there were no significant differences in demographics. Neither thioridazine nor placebo improved the behaviour of the participants. The TSA scale showed that thioridazine increased violence, anger and provocativeness as compared to baseline. Violence and anger also increased in intensity and frequency. Thioridazine reduced the frequency of hyperactivity. Thioridazine was inferior to placebo ($p= 0.06$) on the CAM scale. Thioridazine failed to improve behaviour on the CGI scale and in fact aggravated the condition of patients.

Comments
The study suggests that thioridazine is ineffective for the treatment of aggression in adults with a learning disability. A score of 8/14 was achieved on quality assessment (3/5 on Jadad criteria). The use of a medication standardisation period provided reliable data on the specific efficacy of thioridazine, separate from medication interactions. However, the method of blinding and randomisation was not stated and the number of participants assigned to each group was not detailed.

Wardell et al. (1958)

Participants
82 participants of whom 26 were relevant from the study group and 15 in the placebo group. Age range is unknown but all participants were described as adults with a LD and significant behavioural problems (e.g. aggression, biting etc.) and all were females.

Intervention
Chlorpromazine (n=26) 100-200mg/ three times a day (average dose 400-600mg/ daily) vs. placebo (n=15).

Method
A prospective, RCT with a double blind, placebo controlled design. There was a 6-week baseline pre-test period, followed by 3 months in either of the experimental conditions at the end of which all medications were discontinued and then a subsequent 2-month post-treatment observation period.

Follow-up
Participants were followed up for 10-minute sessions throughout the day and monthly for two separate assessments. The length of follow-up was 3 months in total.

Outcomes
Assessments were conducted using two separate, simultaneous rating methods.

1. Verbal descriptions of behaviour change by the ward attendant in charge, which were then reviewed by two of the investigators and rated for the degree of improvement on a 5-point scale (1 = worse to 5 = markedly improved).
2. Refinement of the previous method whereby toileting, bathing, dressing, social relations and feeding behaviours were chosen to be observed to identify which behaviour involved the most disruptions. Narrative descriptions were categorised from 1 (most efficient behaviour) to 5 (least efficient and most disrupted behaviour).

Results
The first method indicated no significant differences between the mean ratings obtained for those on medication or placebo. Overall, the ward became quieter and pleasant during administration. Analysis for the second rating method was only conducted for those participants for whom reliable pre-test, test and post-test observations were available. There were no significant behavioural changes observed in either of the routine behaviours, with the exception of bathing behaviour in which the chlorpromazine group became worse in the post-test period ($p<0.001$). Side effects were largely reported for the medication group but this may have been a consequence of the ward attendants being able to guess the experimental conditions.

Comments
This study showed negative findings in that there was no improvement in behaviour with medication. This was a very weakly designed study since there were no validated outcome measures employed; although in fairness, many of the outcome scales used to assess behavioural changes were developed after 1958 and the authors did propose that an objective rating scale needed to be developed in the absence of any being available. The authors themselves have indicated that this may not have been a truly double blinded study because it was discovered that the assessors could indeed, almost accurately predict the experimental conditions, which disapprovingly flaws the study. Experimental bias and subjectivity issues question the validity of this study. This study therefore, achieved a rating of 6/14 on quality assessment (3/5 on Jadad criteria).

Adults and Children

Vanden Borre et al. (1993)

Participants
37 children and adults, but only 30 were included after 7 dropped out. Age range 15-58 years (gender ratio unspecified). All participants had DSM-III-R diagnosis of a LD - most were severe or profound. Persistent behavioural problems such as hostility, aggressiveness, irritability, agitation, hyperactivity, auto mutilation and autism were the various target behaviours that participants demonstrated.

Intervention
Risperidone 4-12mg/day (mean dose 8.3mg/day) as an add on vs. placebo (oral matching solution). Duration of treatment was 3 weeks.

Method
A prospective, RCT with a double blind, placebo-controlled, crossover design. There was a 1-week observation period (no intervention) followed by 3 weeks of double blind treatment with either risperidone or placebo. After a 1-week single-blind placebo washout period, there was a further 3 weeks of crossover treatment.

Follow-up
There were weekly follow-up intervals, with the length of follow-up being 8 weeks in total.

Outcomes
1. Primary outcomes were assessed weekly using ratings on the ABC checklist carried out by nursing staff.
2. Behavioural changes were also measured with the CGI-scale and VAS.
3. Adverse reactions were assessed at the end of each double blind period using the Extrapyramidal Symptom Rating Scale (ESRS).
4. Bloods tests, ECG, blood pressure and weight measurements were also conducted.

Results
ABC ratings showed that there was a similar response to placebo (15.4% decrease in score) and risperidone (16.2%) at the first double blind phase. At the second double blind phase, there was a decline in the ABC score for the risperidone group (27.5% decrease in score) and no effect at all in the placebo. The CGI scale showed a significant period effect after one week of treatment ($p<0.05$) and a significant treatment effect from the first week of treatment onwards (weeks 1 and 2: $p<0.05$; week 3: $p<0.01$) in both phases of the crossover trial. There were no significant changes observed on VAS, in general, there was improvement with risperidone and deterioration under placebo. ESRS showed no change between groups. Adverse reactions of sedation (reported 10 times) and drowsiness (reported 6 times) emerged

under risperidone treatment but not whilst on placebo. Bloods and ECG showed no change.

Comments
Risperidone treatment was found to be significantly superior to placebo, although there was no improvement in the risperidone group in the first 3 weeks of the RCT. However, it is unknown how many participants were allocated to placebo or medication. The IQ levels or gender ratio were not specified and the methods of randomisation and blinding were not described. The target behaviours were variable, and a washout period of 1 week and the overall follow-up period of 8 weeks are both very short indeed. The sample size is small and the study is likely to be underpowered. No improvement in the first 3 weeks before crossover makes the data difficult to interpret. This study achieved 9/14 on quality assessment (3/5 on Jadad criteria).

Aman et al. (1989)

Participants
22 institutionalised children and adults, but 20 included after 2 dropped out. Age range was 12.8-35 years (70% male). All participants were described as 'moderately to profoundly retarded' (IQ range 8-48) and the target problem behaviour was stereotypy.

Intervention
Haloperidol low dose (average dose 0.025mg/kg/day) vs. high dose (average dose 0.05mg/kg/day) vs. placebo. The length of treatment for each dose was 3 weeks.

Method
A prospective RCT with a double blind, placebo-controlled, crossover design. There was a 2-week washout period prior to the treatment phases after which participants received 3 weeks of low dose then high dose haloperidol treatment or vice versa.

Follow-up
Follow-up occurred weekly when assessments were made. It appears that the overall study lasted for approximately 8 weeks although the entire time period for the study is not stated.

Outcomes
Nursing staff carried out the following behavioural assessments:

1. ABC ratings weekly.
2. The Fairview Problem Behaviour Checklist (FPBC) for symptoms rating the frequency of problem behaviours (stereotypy and self-injury subscales were only used) at the end of each treatment phase.
3. Direct observations were made for 30-minute sessions each week recording 6 categories of behaviour found to occur in moderate to high frequencies.

4. Physiological measures (heart rate and blood pressure) on the last 3 days of each treatment phase.

Results
ABC ratings showed that stereotypic behaviour was significantly changed due to intervention but there was no significant difference between conditions. The FPBC indicated no change in stereotypy or self-injurious behaviour. Direct observations revealed that movement was increased due to medication, more so in the high dose condition than compared to both the low dose and placebo conditions ($p<0.05$). Inactivity was decreased largely in the high dose condition. Physiological measures remained unchanged. Those participants who initially presented with high levels of stereotypy achieved a more favourable response with haloperidol, whereas those with low stereotypy deteriorated.

Comments
Haloperidol was found to be minimally effective, with the main results indicating improvement with a high dose. Many participants were already receiving neuroleptics prior to this study, and so this could have influenced the results. This study used a small sample size and there was no washout period between the two treatment phases. Blinding procedures are not well described. This study scored 7/14 on quality assessment (4/5 on Jadad criteria).

Vaisanen et al. (1981)

Participants
30 participants, age range 17-46 years (67% male). All participants had a diagnosis of a LD (7 moderate and 23 severe) and were receiving high doses of neuroleptics due to restlessness and related behavioural problems prior to the initiation of the study.

Intervention
Haloperidol 10-60mg/ daily vs. thioridazine 100-600mg/ daily and vs. placebo. Length of time on treatment was 6 weeks for each medication.

Method
The participants were randomly assigned to receive haloperidol then thioridazine or thioridazine then haloperidol with 6 weeks of each treatment. There was a 2-week washout period prior to the trial when previous medication was stopped. Furthermore, a 2-week placebo washout period intervened the two 6 week medication phases and followed the second medication phase. All medications were administered in a double blind manner.

Follow-up
The participants were assessed daily with regards to treatment effects and side effects

Outcomes
Personnel within the institution carried out the assessments. An independent physician from outside the institution also assessed participants at the end of each 2-week period.

1. Primary outcome was a rating sheet specifically designed for the present study. The rating sheet had five symptoms (motor restlessness, self-inflicted injury, hostility and aggressivity, tearing and breaking down of material and psychotic traits) each rated from 0-3 depending on severity.
2. Secondary outcome was global assessment rated from 0 +/- 3 (better/worse).
3. Side effects were also assessed using the extra-pyramidal symptoms rating scale and an informal rating of 0-3 for specific side effects (tiredness, dystonia, dyskinesia and tremor).

Results
The participants were split into two groups, depending on their reaction to the treatment. There were 13 responders to both medications, 8 to haloperidol only and 6 to thioridazine only. 3 participants were classed as medication non-responders. The responders became significantly better and non-responders became significantly worse with haloperidol or thioridazine. There were few differences in side effects between the two treatments.

Comments
Due to there being responders and non-responders and rather confusing statistics quoted, it is difficult to form an interpretation of efficacy for either medication. The blinding techniques were not specified and the primary outcome assessments were un-validated. Furthermore, the crossover design leads to difficulties with carry-over effects, which may not have been adequately controlled for by the two-week placebo washout period. This study achieved 7/14 on quality assessment (4/5 on Jadad criteria).

Vaisanen et al. (1975)

Participants
60 inpatients, age range 8-40 years (gender ratio unspecified). 9 had a moderate LD, 25 severe and 26 profound. All participants presented with restless behaviour and other related behavioural problems.

Intervention
Sulpiride 50-100mg/t.i.d. vs. chlorpromazine 25-50mg vs. placebo. Medication was given for 4 weeks each.

Method
A prospective RCT with a double blind, placebo-controlled, crossover design. There was a 5-day washout period prior to the study followed by 4 weeks of each treatment.

Follow-up
Participants were assessed daily by the personnel and 4 times during the trial period jointly by a physician, psychologist and ward personnel.

Outcomes
1. Daily ratings were recorded on a rating sheet designed for the study itself which measured 7 variables in terms of intensity and incidence: motor restlessness, self-inflicted damage, violence, tearing and breaking down of materials, anxious yelling and reluctance
2. Global assessment rated on a 7-point scale.

Results
Behaviour was changed towards a more positive direction when sulpiride replaced placebo as indicated on the global assessment scale only ($p<0.05$). Sulpiride was found to be as effective as or possibly superior to chlorpromazine ($p<0.1$).

Comments
Sulpiride was found to be of limited efficacy and not much different to chlorpromazine. This was a very weak study in that it did not use validated outcome measures and furthermore, did not describe the 7-point global assessment scale. The method used for selecting participants did not appear to be randomised in itself and this was based on the ward personnel's judgements as to who should/ should not be included. There was no washout period between the two medication phases and it is unclear on how randomisation was conducted. This study achieved 4/14 on quality assessment (2/5 on Jadad criteria).

Weir et al. (1968)

Participants
45 inpatients, average age 17.0 years (sd 5.1) for females and 13.1 years (sd 5.1) for males (49% male). IQ levels were 50+ for n=15, 20-49 for n=15 and 0-19 for n=15. All were described as 'disturbed, mentally subnormal participants'.

Intervention
Pericyazine vs. chlorpromazine vs. placebo. Doses are unknown. Each condition lasted for 12 weeks.

Method
A RCT, with a double blind, placebo controlled design. A 6-week washout period preceded the study. Participants were split into two groups, in group one pericyazine was administered for 12 weeks followed by 12 weeks of an inert solution (placebo) or vice versa. The second group followed the same procedure but this time chlorpromazine was given.

Follow-up
Assessments took place daily and it appears that the overall trial lasted for 30 weeks (including the 6 weeks prior to the study).

Outcomes
1. Daytime assessments were conducted by senior nurses who rated behaviour on an amended version of a behaviour scale adapted from another study. This used a 4-point scale (1 = behaviour occurred to a marked degree, 4 = not at all).
2. Night time behaviour was assessed on a scale developed by the investigators themselves.

Results
There were 2 withdrawals from this study. The ratings on the day scale were analysed using two different methods but either method did not find any significant difference between either of the medication groups or placebo. There was a difference between the pericyazine vs. no intervention groups ($p<0.025$, $p<0.01$) and between chlorpromazine vs. no intervention ($p<0.005$, $p<0.01$). The chlorpromazine group also indicated a difference between placebo and no intervention ($p<0.025$, $p<0.01$). The night scale remained unchanged as did weight and liver function tests.

Comments
There are no convincing effects demonstrated of medication over placebo. This study is of very poor quality as there is a lot of important data missing. It is unknown what the dosages were, whether or not there was a washout period between treatment and placebo and whether the differences that have been highlighted refer to changes in terms of improvement with medication or deterioration. There are no specific behaviours targeted and the night time behaviour rating scale has not been described. This study achieved 8/14 on quality assessment (2/5 on Jadad criteria).

Children

Shea et al. (2004)

Participants
79 children, age range 5-12 years (77% male) with pervasive developmental disorders. 28% had a moderate LD and 25% mild; hence 53% of the sample had a LD. All participants presented with various behavioural symptoms including aggression and tantrums.

Intervention
Risperidone (n = 40) 0.01 mg/kg/day – 1.48 mg/day (mean dose 1.17 mg/day) vs. placebo (n = 39).

Method
Randomised, multi-centre, double blind, placebo-controlled trial (parallel design).

Follow-up
Over the 8-week trial period, the participants had 7 follow-ups: at baseline, and then at weeks 1, 2, 3, 5, 7 and 8.

Outcomes
1. ABC completed by the parent or caregiver.
2. Parent version of the Nisonger Child Behaviour Rating Form (NCBR-F).
3. VAS for the most troublesome symptom completed by the parent or guardian.
4. CGI-Change scored by the investigator.
5. Safety measures including the examination of vital signs, weight gain and assessment on the Extrapyramidal Symptom Rating Scale (ESRS) for extrapyramidal symptoms.

Results
Data was analysed using the intention-to-treat principle. Of the 79 participants, 72 completed the study; 2 of the withdrawals were from the risperidone group and 5 from placebo. ABC-irritability subscale scores at endpoint revealed that there was a 64% improvement in the risperidone group vs. 31% in placebo ($p<0.001$). Significant improvement was also apparent according to other subscales of the ABC ($p<0.05$), NCBR-F subscales (conduct problem subscale: $p<0.01$) and VAS ($p<0.05$) on which the most frequently reported symptom was aggression (23.4%). CGI global improvement at endpoint was 87% in the risperidone group vs. 40% in placebo ($p<0.001$). Adverse effects revealed that extrapyramidal symptoms were comparable between the two groups, weight gain with risperidone was 2.7kg vs. placebo 1kg ($p<0.001$), and somnolence with risperidone was present in 73% vs. placebo 8%.

Comments
This study scored 3/5 on Jadad quality assessment and supports the use of risperidone among children. Nonetheless, it may be low powered and although mentioned, the methods of randomisation and blinding are not described in detail. A follow-up period of 8 weeks is too short but does highlight the occurrence of adverse events over such a short time period, which is a cause for concern.

Aman et al. (2002)

Participants
118 children, age range 5-12 years (82% male). 17% had a moderate LD, 32% mild and 51% borderline. All presented with various disruptive behaviours, some of which included aggression, hyperactivity, SIB and stereotypy.

Intervention
Risperidone (n = 55) 0.02-0.06 mg/kg per day (average dose 1.16mg/ day) vs. placebo (n = 63). A dose of greater than 0.06mg/kg per day was administered in 4 of the participants.

Method
Randomised, multi-centre, double blind, placebo-controlled trial (parallel design).

Follow up
The participants were assessed at weekly intervals and the overall follow-up period was 6 weeks.

Outcomes
1. Primary efficacy measure was the Nisonger Child Behaviour Rating Form (NCBR-F; conduct problem subscale) from baseline to endpoint.
2. Secondary efficacy measures were the other NCBR-F problem behaviours section subscales as well as the social competence section subscales, ABC, Behaviour Problems Inventory (BPI), VAS and change scores on the CGI.
3. Weight gain, vital signs and extrapyramidal symptoms were also assessed weekly.

Results
Analysis was conducted on an intention-to-treat basis. 43 (78%) and 44 (70%) completed the study from the risperidone and placebo groups respectively. The reasons for those withdrawn were variable including insufficient response to medication and non-compliance.
The risperidone group showed a significant decrease in NCBR-F conduct subscale scores (change in score at endpoint –15.2) than did the placebo (–6.2). In the risperidone group, problem behaviour ratings significantly decreased and pro-social behaviours increased according to the social competence subscale. There was significant improvement in the ABC-irritability, hyperactivity, lethargy subscales, BPI-aggressive, destructive behaviour subscales, CGI ($p<0.001$) and VAS (at week 6: $p<0.05$). 40 (76.9%) and 21 (33.4%) were rated as improved on the CGI in the risperidone and placebo groups respectively. 54 (98%) and 44 (70%) reported adverse events in the risperidone and placebo groups respectively. Common adverse effects were headache and somnolence (not extrapyramidal symptoms) with risperidone. Mean weight gain in the risperidone group was 2.2kg vs. placebo 0.9kg.

Comments
This was a good quality study achieving 3/5 on Jadad assessment and supports the use of risperidone among children. The main shortcomings of this study were that the methods of randomisation and allocation concealment were not well described and the follow-up period was short, although this can be accounted for by the fact that significant clinically, therapeutic effects were seen as early as the first week of medication.

Research Units on Pediatric. Psychopharmacology. Autism Network. (2002)

Participants
101 children, age range 5-17 years (81% male). All met DSM-IV criteria for autistic disorder, 31% had a severe LD and 43% mild/moderate. The participants presented with behavioural problems including tantrums, aggression and self-injurious behaviour.

Intervention
Risperidone 0.5-3.5mg/ day (n = 49) vs. placebo (n = 52). Average daily dose of medication was 1.8mg.

Method
Randomised, multi-centre, double blind, placebo-controlled trial (parallel design).

Follow-up
Participants were assessed weekly for a total of 8 weeks.

Outcomes
1. ABC irritability subscale ratings performed by parents/ primary caretakers.
2. CGI-Improvement ratings carried out by a clinician.
3. Clinicians using the Simpson-Angus scale and Abnormal Involuntary Movement Scale (AIMS) assessed any neurological side effects.

Results
Data was analysed using an intent-to-treat principle. There were 4 withdrawals (3 in the risperidone group and 1 in placebo). An additional 17 in the placebo group failed to complete the study due to various reasons including the lack of efficacy and consent withdrawal. The risperidone group had a 56.9% reduction in ABC irritability score vs. placebo 14.1% ($p<0.001$). CGI-I much or very much improved ratings were made for 69% in the risperidone group vs. 12% in placebo ($p<0.001$). Average weight gain was 2.7±2.9kg with risperidone vs. 0.8±2.2kg with placebo ($p<0.001$). Increased appetite, fatigue, drowsiness, dizziness and drooling were more common in the risperidone group ($p<0.05$). Tremor was common in the risperidone group ($p=0.06$) but otherwise, no extrapyramidal side effects were reported.

Comments
This study supports the use of risperidone among children. However, the methods of randomisation and concealment are not well described and the follow-up period is short. This study scored 3/5 on Jadad quality assessment.

Snyder et al. (2002)

Participants
110 children, age range 5-12 years (75.5% male). 48.2% had borderline IQ, 38.2% mild and 13.6% had a moderate LD. 41 (37.3%) had conduct disorder, 69 (62.7%) had oppositional defiant disorder or destructive behaviour disorder not otherwise specified and 84 (80%) had comorbid ADHD. All presented with various behavioural problems such as aggression, impulsivity, defiance of authority figures and property destruction.

Intervention
Risperidone (n=53) 0.40-3.80mg/day (average dose 0.98 mg/d) vs. placebo (n=57).

Method
A randomised, double blind, placebo-controlled (parallel-arm comparison) trial. Following a 1-week single blind placebo period prior to the study, the participants were randomly assigned to receive either medication or placebo.

Follow-up
Participants were assessed at baseline and then weekly. The total follow-up period was 6-weeks.

Outcomes
1. The Conduct Problem subscale of the Nisonger Child Behaviour Rating Form (NCBR-F) for problem behaviours was assessed weekly as a primary measure.
2. Subscales of the ABC, BPI, CGI, and VAS of the most troublesome symptom and VAS of sedation were all used as secondary measures.
3. Cognition was also assessed using the Continuous Performance Task (CPT) and verbal learning by means of the California Verbal Learning Test for children (CVLT).
4. Extrapyramidal symptoms were assessed with the ESRS.

Results
Analysis was conducted on an intention-to-treat basis however, 25 (23%) of the participants withdrew from the study, 19 (33%) from placebo and 6 (11%) from the risperidone group. There were highly significant changes on the Conduct Problem subscale of the NCBR-Form ($p<0.001$); reduction in symptom rating for the placebo group was 6.8 (20.9%) compared to 15.8 (47.3%) for the risperidone group at endpoint. There were significant improvements on all subscales of the ABC. The BPI only demonstrated significant differences for the aggressive behaviour subscale ($p<0.01$): 21.5% reduction in the scores for placebo and 45.9% for risperidone. The VAS/ symptom scale showed a greater reduction in the scores for risperidone (37.4%) than placebo (15.8%) ($p<0.001$). At endpoint, 14 (25%) on placebo and 42 (77%) on risperidone were rated as improved to some degree on CGI ($p=0.001$). 42 (73.7%) in the placebo and 46 (86.8%) in the risperidone group experienced at least one adverse event. Commonly reported side effects included somnolence, headache, appetite increase and dyspepsia.

Extrapyramidal effects were noted in 7 (13.2%) and 3 (5.3%) in the risperidone and placebo groups respectively (p=0.245). There was a 2.0kg weight gain observed in the risperidone group and 0.2kg in the placebo (p<0.001).

Comments
Overall, this was a well-conducted study supporting the use of risperidone in children with behaviour problems, scoring 4/5 on quality assessment. However, randomisation and allocation concealment methods were not well described and a 6-week period is a very short duration for follow-up. Due to the high rate of attrition it is likely that it might have become apparent to the assessors who was in the treatment group and who was not.

Buitelaar et al. (2001)

Participants
38 children, age range 11.7-15.7 years (87% male). 14 had subaverage IQ, 14 with borderline and 14 with mild a LD. All participants had IQ between 60-90 and were institutionalised at the time of the study for severe aggressive behaviour that was intractable to previous interventions including behavioural treatments. 26 (68%) of the participants had a co-morbid diagnosis of ADHD.

Intervention
Risperidone (n=19) 1.5-4mg/ daily (average dose 2.9mg/ daily) or a matching placebo (n=19). All previous treatments were discontinued at the initiation of the study except for those managing extrapyramidal symptoms.

Method
A randomised, double blind, placebo controlled (parallel-arm comparison) trial. There was a 2-week baseline period before the study and a 2-week washout at the end of the 6-week double blind phase whereby risperidone and placebo were stopped.

Follow-up
The participants were assessed at the end of the 2-week baseline period, and then at weeks 2, 4 and 6 (endpoint) during the double blind phase and at the end of the 2-week washout phase. Hence, the overall duration of the trial appears to be 8 weeks.

Outcomes
1. Primary outcome measure was the CGI - Severity of Illness scale, measured by the prescribing psychiatrist.
2. Secondary outcome measures were the Modified Overt Aggression (OAS- M) scale and the ABC measured by ward personnel and teachers.
3. The Extrapyramidal Symptom Rating (ESRS) scale was used to assess any adverse effects.

Results
Analysis was conducted on an intention-to-treat basis. On the CGI-S scores, risperidone was found to be statistically superior to placebo ($p=0.013$) after 2 weeks and throughout the whole treatment phase thereafter.
The overall OAS-M scores demonstrated that risperidone significantly reduced aggression ($p<0.01$), and the sub-scales of physical aggression ($p<0.001$) and aggression to property ($p<0.01$) also showed a significant reduction at endpoint. No significant differences were found in the placebo group. The difference in changes between the two groups however, failed to reach significance at the 0.05 level. The risperidone group had overall ABC scores that significantly improved ($p<0.05$) at endpoint compared with baseline. Furthermore, there was a significant deterioration of these scores during washout ($p<0.05$). There were no significant changes in the ABC scores for the placebo group.
Adverse events were reported by 17 (89%) in the risperidone group and 11 (58%) in the placebo, with tiredness being the common side effect. Overall, ratings on the ESRS were low, with the exception of Parkinsonism, which was increased in the risperidone group only ($p<0.05$).

Comments
This was a well-designed study and adequately described randomisation and blinding techniques, and thus, achieved a score of 5/5 on Jadad quality assessment. Personnel and teachers received training on how to administer the ratings which adds value to the outcome assessments. The main drawbacks of this study are the small sample size and the very short follow-up period of 6 weeks, which does not allow inferences to be made as to whether the effects achieved within this study would be maintained in the long-term.

Prospective studies

Adults and children

Zarcone et al. (2001)

Participants
20 adults and children participants, 25% were 6-12 years of age, 30% 13-18 years and 45% were 19-65 years of age. 50% were male. 10% had a mild LD, 40% moderate, 25% severe and 25% profound. All participants had an IQ level below 70. Most participants had a co-morbid illness as well. Aberrant behaviours such as severe SIB, aggression, property destruction and stereotypy were the target behaviours.

Intervention
Risperidone was given to all participants at both a low dose (average doses - children/adolescents: 1mg/day, adults: 2mg/day) and a high dose (average

doses - children/adolescents: 1.8mg/day, adults: 4.52mg/day), each for a period of 4 weeks.

Method
Although classified as a prospective RCT with a double blind, placebo-controlled, crossover design, this study does not qualify as a proper crossover trial. Instead of medication being given parallel to placebo, as one would anticipate in a crossover trial, this study has high vs. low dosages of medication, with two separate placebo periods. Thus, this study has been considered as a prospective trial rather than a RCT. The phases of the study were an initial baseline/washout period in which all previous medication was tapered and discontinued, unless the participant was on seizure or other physically indicated medication. A placebo 1 period, then a high/low dose phase and then finally placebo 2 and maintenance phases followed this.

Follow-up
Follow-up was either bi-weekly or at the end of each study week. Overall, length of follow-up was 22 experimental weeks with a 6-months follow-up period.

Outcomes
1. At the end of each study week, ABC-Community ratings, Nisonger Child Behaviour Rating Form (for children only) and a 25-item Self Injurious Behaviour Questionnaire (for adults only) were completed by the caregivers.
2. A psychiatrist performed CGI assessments bi-weekly.
3. Tardive dyskinesia (TD) symptoms were measured using the Dyskinesia Identification System: Condensed User Scale (DISCUS) bi-weekly also by the psychiatrist.
4. Caregivers completed the neuroleptic side effects checklist bi-weekly.

Results
Mainly the medication effects were evaluated using ABC-C scores in each placebo phase versus the total score of high/low dose phases. Mean ABC-C ratings showed lower scores occurred in the second phase of the medication sequence regardless of whether the sequence was low dose to high or vice versa (no significant dose effect at 0.05 level for the medication sequence was apparent). The NCBR-Form ratings on the conduct scale for children demonstrated better effects on high doses of risperidone. For the NCBR-SIB subscale, there were greater reductions in aberrant behaviour whilst on the low dose. Mean ratings on the SIB-Q for adults showed that overall there was a reduction in behaviour on the low doses of risperidone and additionally, behaviour improved during the second phase. CGI scores showed similar results across medication phases. There were no TD symptoms observed. Weight gain (84%) and sedation (50% on low dose and 47% on low dose) were significantly increased whilst on medication.

Comments
The study design is complicated and therefore the results are confusing to interpret. It is unclear why high and low doses of risperidone were

administered if the overall purpose of the study was to compare risperidone with placebo. It does appear that the study is indeed comparing low with high doses of medication rather than with placebo. The study does mention that caregivers were not blinded to the conditions of the study and this could have influenced their ratings. The SIB-Q is not a validated outcome measure. This study achieved 8/14 on quality assessment.

Adults

La Malfa et al. (2003)

Participants
15 participants, age range 25-47 years (66.7% male). 33.3% had a mild LD, 33.3% moderate, and 33.3% severe. All had associated behaviour problems and psychotic illnesses (5 had explosive disorder, 3 Pervasive Developmental Disorder (PDD), 4 Schizophrenia and 2 bipolar disorder).

Intervention
Quetiapine 300-1200 mg/day. Treatment duration was 6 months.

Method
Prospective case series.

Follow-up
Participants were assessed at baseline, at 3 months and then at 6 months.

Outcomes
1. The Handicaps Behaviour and Skills Schedule (HBSs) for behaviour.
2. The Dosage Record Treatment Emergent Symptom (DOTES) scale for side effects.

Results
Treatment significantly reduced the overall scores on the HBSs. A greater improvement was shown in those with a mild to moderate LD - reduction between baseline and final assessment was 63.1% for participants with a mild LD, 55.2% for moderate and 25.9% for severe LD. On DOTES, the major side effects were sedation, increase in appetite, and weight gain but all were of low incidence and so discontinuation of medication or adjuvant therapy was not necessary.

Comments
The study is limited by the lack of a control group and small sample size. HBSs total scores are provided rather than individual behaviour specific scores. Follow-up was for a reasonable period and the participants had associated psychiatric illness. This study was rated as 4/9 on quality assessment.

La Malfa et al. (2001)

Participants
18 participants, age range 24-39 years (67% male). 55.6% had a mild LD, 22.2% moderate and 22.2% severe. The target behaviour was aggression.

Intervention
Risperidone (average dose 2 mg ± 1 mg/day). Treatment duration was 3 months.

Method
A prospective, open label study.

Follow-up
Assessed at baseline and then at 3 months.

Outcomes
1. Handicaps Behaviour and Skills Schedule (HBSs) for aggression.
2. Psychopathological Instrument for Mentally Retarded Adults (PIMRA).
3. The Clinical Global Impression (CGI) Scale.

Results
The total HBSs score before treatment was 13.44 (sd 5.31) and after 4.39 (sd 3.20); $p = 0.0002$. The PIMRA score before treatment was 26.78 (sd: 5.90) and after 14.83 (sd 6.38); $p = 0.000$. Total CGI score before treatment was 6.17 (sd 0.17) and after 2.56 (sd 1.46); $p = 0.000$. Therefore, all 3 scales showed an improvement after 3 months of treatment.

Comments
There was no control group used and the sample size was small. There was no specific behaviour measure. Follow-up was for a reasonable period. This study scored 4/9 on quality assessment.

Lott et al. (1996)

Participants
39 participants (but 6 were lost to follow-up and their data has not been included). Age range 25-66 years (69.7% male). 9% had a mild LD, 9% moderate, 15% severe and 67% profound. 42% had PDD, 6% bipolar disorder and 6% psychotic disorder not otherwise specified. The presenting behaviours were aggression or assault, SIB with or without injury and property destruction.

Intervention
Risperidone 1-8 mg/day (mean dose 5.1 mg) as an add on. Length of treatment was at least 6 months.

Method
Prospective case series.

Follow-up
Participants were assessed monthly for 6 months before and 6 months during treatment.

Outcomes
1. Objective frequency counts of targeted behaviour (aggression or assault, SIB, SIB with injury and property destruction).
2. Staff assessments of patients' global status (considering the behaviour frequency, severity and overall functional status rated as improved, no change, or worse) and side effects.
3. Consulting Psychiatrist's clinical assessment.
4. Side effects.

Results
61% of the participants showed a 50% or greater reduction in the frequency of one or more target behaviours. Global response: after 6 months of treatment, 85% improved and 15% remained unchanged. Before treatment, assault/ injury to staff totalled 43 assaults by 15 patients resulting in them losing at least 444 days off work. After treatment, there were 20 assaults by 6 patients resulting in 29 workdays being lost. Noted side effects were sedation 12%, weight gain 9%, pseudoparkinsonism 12% and akathisia 9%. No side effects were severe enough to warrant discontinuing treatment.

Comments
There was no control group used and the sample size was small. Outcome was based on the global assessment carried out by the staff and frequency ratings of the target behaviours for which the method of frequency recording is not described. Outcome measures were therefore not validated and no statistical analysis is presented. Participants had associated psychiatric illness. This study scored 7/9 on quality assessment.

Gualtieri et al. (1990)

Participants
15 participants of whom 12 were adults and so the data for them is reported here. Age range 18-46 years (25% male). All had a severe to profound LD and had a long history of SIB.

Intervention
Fluphenazine 0.5mg b.d. - 15 mg/day.

Method
Prospective case series.

Follow-up
Participants were followed-up weekly and then monthly for a period of 18 months to 3 years.

Outcomes

1. The Aberrant Behaviour Checklist (ABC) and Clinical Global Impression (CGI) were abandoned due to insensitivity in favour of the "Individual Behaviour Observations" (IBO) by parents and unit Psychologists.
2. Neuroleptic Side Effects Checklist was completed by nurses or parents.
3. Physicians used the Simpson-Angus Extra-Pyramidal Symptoms (EPS) Ratings and Abnormal Involuntary Movements Scale (AIMS) monthly.

Results

Based on the IBO ratings, 9/12 (75%) that benefited from the treatment were classified as responders and 3/12 (25%) who showed no benefit at all were classified as non-responders. Furthermore, 3/12 (25%) were classified as low dose responders because titrating fluphenazine downwards yielded better responses, higher doses were related to akathisia symptoms which aggravated the SIB. Extrapyramidal side effects were noted in 4/12 (33%) participants of whom 3 (25%) also experienced akathisia.

Comments

The sample size is small and no control group is used. Good case histories of each participant are provided but the effect of other concurrent medications is not known. The IBO outcome measure is not validated and the definition of respondent is arbitrary. The follow-up was for a good length of time. The study showed that the high dose antipsychotics might make behaviours worse in some participants by causing extrapyramidal adverse effects. This study scored 7/9 on quality assessment.

Retrospective studies

Thalayasingam et al. (2004)

Participants

24 participants, age range 26-56 years (71% male). 8% had borderline intellectual functioning, 71% mild and 21% moderate. No patients with a severe or profound LD were included. 8% had PDD, 13% personality disorder, 33% substance abuse, 21% epilepsy, 67% schizophrenia, 17% schizo-affective disorder, 8% bipolar affective disorder and 8% had no diagnosable mental illness. A risk assessment was carried out for each of the participants using the overt aggression scale (OAS), which revealed various aggression related problems.

Intervention

Clozapine 300-800 mg/day (mean maximum dose 485 mg/day). Treatment was given for a mean duration of 45 months (sd 33.5, range 12-132 months).

Method
Case note based study reviewing notes of patients from 3 settings by 2 independent investigators.

Follow-up
-

Outcomes
Global improvement efficacy index scores of the CGI scale were used to measure behaviour and any side effects.

Results
29% of participants were rated as very much improved, 42% as much improved, 21% as minimally improved and 8% remained unchanged. There were also improvements on other parameters: 54% of the total sample was discharged to the community and 53% were discharged from medium secure units. As far as side effects were concerned, neutropenia occurred in 17% of the patients, drowsiness 21%, weight gain 21%, increased salivation 13% and extrapyramidal side effects in 8%.

Comments
There was no control group, the sample size was small and results based on CGI assessments from retrospective case notes are not sufficient to be deemed reliable. No validated outcome measure has been used. The definition of improvement is not clear or validated. Most participants had associated psychiatric illness and so the effect is likely to be on psychosis rather than specifically on behaviour problems. This study scored 3/9 on quality assessment.

Janowsky et al. (2003)

Participants
20 participants, age range 18-55 years (45% male). The majority were in the severe to profound IQ range and had a LD. The target behaviours were aggression, SIB and destructive/ disruptive behaviours or combinations of these. Co-morbid psychiatric diagnoses had also been assigned to the majority of the participants.

Intervention
Olanzapine 2.5-22.5mg/day (maximum mean dose 9.1 mg/day) as an add-on. Length of treatment was up to 6 months.

Method
Summaries were examined of quarterly neuropsychiatric behavioural review (NBR) conference reports and retrospective reviews of longitudinal behavioural graphs of target symptoms.

Follow-up
Participants were assessed at 6 monthly intervals for at least 1 year.

Outcomes
Unit Psychologists assessed the target behaviours.

1. Behaviours were measured as a cumulative frequency for 6 months before and after medication initiation.
2. Global behaviour was rated on a 7-point scale (1 = no symptoms to 7 = severe symptoms) based on the NBR.
3. Side effects were reported as part of the NBR.

Results
Aggression displayed in 14 participants decreased in 93% ($p<0.01$) and SIB displayed in 7 participants decreased in 86% ($p<0.044$). Disruptive and other behaviours displayed in 11 participants decreased in 73% ($p<0.021$). 80% showed a decrease in the global ratings, 15% showed an increase and 5% showed no change. Side effects were reported as follows: sedation in 4 (20%), constipation in 2 (10%), gait problem in 1 (5%) and pre-olanzapine weight was 68.2 kg and post-olanzapine 72.0 kg ($p<0.006$). No increase in serum glucose levels was seen.

Comments
No control group has been used. The sample size is small and the case selection method is unclear. The outcome measures are not validated and therefore, may be prone to bias. Bias is also introduced by the retrospective nature of the case notes study. Most participants had associated psychiatric illness. This study scored 6/9 on quality assessment.

Boachie et al. (1997)

Participants
17 participants, age range 20-46 years (65% male). 70.6% had a mild LD, 23.5% moderate and 5.9% severe. 15/17 had schizophrenia. Participants presented with various behavioural problems including aggression and SIB.

Intervention
Clozapine 200-900 mg/day (average dose 640 mg in females, 357.1 mg in males). Length of treatment was an average of 32.1 months (range 9-47 months; sd 11.9).

Method
Examination of case notes and medication charts of participants.

Follow-up
Follow-up was 3 years.

Outcomes

1. Participants' response to clozapine was clinically rated on a 4-point clinical observation scale (markedly improved, improved, no change or worse).

2. Secondary outcomes were more objective because they either occurred or did not.

Results
47% of the participants were rated as 'markedly improved' and 29% as 'improved'. The other 24% showed no improvement or became worse on clozapine.

Comments
There is no mention of who did the outcome assessment and there is no mention of the use of any specific objective scale. Most participants had psychosis and so the effect may be on this rather than on a specific behaviour problem. Bias is introduced by the retrospective nature of this study. This study scored 4/9 on quality assessment.

Table 1: Studies excluded on full text

Study	Summary	Reason for exclusion
Advokat, 2000	Survey type study comparing the side effect profiles of typical and atypical antipsychotics using the Matson Evaluation of Drug Side Effects (MEDS) scale in people with a LD. The overall conclusion was that persons with a LD on atypical antipsychotics show fewer adverse events and experience a shorter duration of adverse events compared to individuals on typical antipsychotics.	There was no antipsychotic medication intervention given to control behaviour and hence, no outcome measures relating to the treatment of behaviour problems.
Aman, 2005	This was a pooled analysis of two parallel RCTs that used identical designs (Aman *et al,* 2002; Snyder *et al,* 2002). The ratings for the Nisonger Child Behaviour Rating Form were combined in order to assess risperidone efficacy. Improvement was established on the social competence and problem behaviour subscales.	Although this study resulted in a larger cohort for analyses, only one outcome scale was assessed. Therefore, the two separate RCTs were included which applied more behavioural outcome measures.
Aman, 1991	This was a RCT of thioridazine, methylphenidate and placebo. 30 children with subaverage IQs and diagnoses of attention deficit disorder (ADD) and/ or conduct disorder were administered each of the interventions. Thioridazine was minimally effective in reducing hyperactivity.	24 of the children were diagnosed with ADD with hyperactivity and it was difficult to tease apart the medication effects for this vs. LD, especially as methylphenidate was given as well, which is indicated for ADD. The outcome measures were also those that are usually used for ADD such as the Conners Teacher Questionnaire.
Aman, 1988	This was a RCT with 11 adults and children. Participants were observed whilst receiving their previous dose of thioridazine and then randomised to either high or low dosages of medication or placebo conditions. There were no significant medication effects between all four conditions.	This is effectively a withdrawal study as participants were withdrawn from their previous dosage and then randomised to the experimental conditions.
Aman, 1984	This was a placebo controlled, crossover study looking at the effects of chlorpromazine in reducing the stereotypic behaviour of 6 participants with a LD. Although the medication was effective in the suppression of body rocking, it did not have an impact on other clinical behaviours.	There were less than ten participants in the study. 2 of the participants were children and there was no separate data for the adults in this study.

Table 1:Studies excluded on full text (continued)

Study	Summary	Reason for exclusion
Bokszanska, 2003	Survey type study looking at the use of atypical antipsychotics in the treatment of psychosis and other mental health problems in people with a LD. This reviewed the prescription trends for olanzapine and risperidone and found that both medications appeared to be safe and effective in managing a range of target symptoms including behaviour problems in people with a LD.	This was a survey and not an interventional study.
Branford, 1996	This study was in three parts looking at tardive akathisia in people with a LD. Part two was the interventional phase, whereby 67/111 participants had their antipsychotic medication dosage reduced. There were no differences found in any of the adverse event scores when compared to participants who did not have a reduction in their medication dosage.	The intervention was investigating the withdrawal of medication.
Burk, 1968	This was a double blind RCT of haloperidol vs. placebo in 50 children with a LD. The medication was more effective than the placebo in improving behaviours such as hyperactivity, assaultiveness, impulsivity and self-injury.	This RCT was carried out before 1990 with no adult participants and thus was not merited for inclusion.
Cohen, 2001	This was a chart review assessing the effect of calorie restriction on weight gain in persons with a LD treated with risperidone. It was concluded that weight gain does not appear to be dose related and that calorie restriction does not lead to weight loss or deterioration in behaviour.	The intervention was calorie restriction treating side effects.
Cohen, 2003	This was a retrospective chart review of 40 patients with a LD and various behaviour problems including assault and self-injury. Participants had been switched to ziprasidone if they had gained weight or were inadequately responsive to other antipsychotics. At 6 months of treatment 48% improved and 28% became worse and at 9 months, 47% improved and 21% became worse.	Ziprasidone is not in the BNF and not available in the UK yet.
Davis, 1969	A RCT of thioridazine, methlphenidate, placebo and no medication conditions in 9 participants with a LD whom displayed continuous stereotypy. Thioridiazine was effective in reducing stereotypical behaviour, without affecting non-stereotypical behaviour.	There were less than ten participants in the study whom were mainly children and so this study was not eligible for inclusion in search 2.

Table 1:Studies excluded on full text (continued)

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. Haloperidol was one of the medications and given as a single dose IM. This appeared to reduce the number of clusters of stereotyped movements observed, but did not modify the duration or frequency of the movements.	This was the only study considering IM treatment that was revealed. The other studies were all concerned with oral treatment and therefore, on this basis it was decided that this study should be excluded.
De Smedt, 2002	This was a prospective, 1-year open label, placebo-controlled study of risperidone following a 2-week minimum double blind phase. ABC scores were lower in the risperidone group compared to placebo; side effects of somnolence, headache and injury were reported.	Only the abstract was available and so not enough information to comment on the quality of the study.
De Smedt, 1999	This was a poster presented prior to the original study published by Van Bellinghen et al. (2001)	Same as Van Bellinghen et al. (2001), this has been looked into in the children's review.
Favazza, 1990	This was a letter reporting on the treatment of self-injurious behaviour associated with a LD with naltrexone.	This was a very brief letter relating to the effects of an opiate antagonist and not an antipsychotic medication.
Ferguson, 1982	This article consisted of four experiments exploring neuroleptic medication effects on IQ scores and habilitative behaviours in 162 participants with a LD. Placebo-controlled, double blind procedures were used during medication withdrawal in each of the experiments and it was concluded that neuroleptics did not reduce inappropriate behaviours and interfered with task performance.	The controlled procedures in this article were only utilised for the medication withdrawal aspects of each experiment.
Franco, 2000	This was an open label, observational study evaluating the safety and effectiveness of risperidone in 127 patients with a LD looking at side effects. Risperidone was generally well tolerated.	There was no intervention used to control a behaviour problem.
Gagiano, 2000	The abstract for this study was in a conference proceeding.	Same as Gagiano, 2005.
Gingell, 1994	This was a retrospective, case series study in which 29 patients suffering from psychiatric illness with a LD on antipsychotic medication were compared to a control group, in order to assess the effect of the medication on the occurrence of movement disorders. Persons given antipsychotics within the BNF guidelines did not show significant increases in movement disorders.	Patients who received antipsychotics mainly to control their behaviour without a psychiatric diagnosis were excluded from the study. No outcomes were reported on behaviour before and after intervention.

Table 1:Studies excluded on full text (continued)

Study	Summary	Reason for exclusion
Glazer, 1997	This article described the use of atypical antipsychotics for a number of psychotic disorders.	This was a review paper.
Gualtieri, 1993	This longitudinal study assessed the effects of treatment on the course of tardive akathisia. The 25 participants included all those who had been diagnosed with this condition including some of whom had a LD, but the exact number is unknown.	There is no antipsychotic medication intervention and no report on behaviour.
Hal, 2004	In this study, 60 participants with a LD were treated with risperidone and evaluated after 3 months using a scale devised for this study. Comparisons were drawn between this group and a matching cohort treated with typical antipsychotics. Risperidone was found to be more effective for several behaviours than typical antipsychotics and associated with a lower rate of side effects.	This paper is in a foreign language (Hungarian) and there is not enough information available in the abstract to assess the quality of the study.
Hassler, 1998	A retrospective, study in which individuals' medications were analysed (10 with a LD). Zuclopenthixol was found to have reduced aggression in 60% of the patients from substantial problems to no problems on a 3-point behaviour modification scale.	This was a retrospective medication withdrawal study.
Hassler, 2002	This was a clinical trial of 20 participants with a LD and aggression or SIB whom were administered risperidone over a period of 35 months. Clinical efficacy as measured by the Disability Assessment Schedule (DAS) showed that 17 participants had a reduction in their target behaviours.	The age range of participants was 15.8-51 years with no separate data for those aged 18 and over.
Heistad, 1979	This was a double blind, placebo-controlled, crossover study looking at the efficacy of thioridazine in 20 participants with a LD. Participants had their medication removed from a stable medication baseline and then the study was initiated. There were some results in favour of thioridazine, but potential methodological problems have been indicated which make the results doubtful.	There is a lack of information reported, including the failure to report relevant demographical data. Furthermore, this is effectively a withdrawal study.
Khan, 1997	This was a prospective trial in 21 participants with a LD and behaviour problems including tardive dyskinesia. Participants who had been switched from conventional neuroleptics to risperidone were followed up until their behaviour was controlled. Clinical observation of 13/21 participants showed marked improvements in their behaviour within 2-3 months.	Although behaviour was mentioned in the study, the primary outcome measures were related to tardive dyskinesia and not behaviour problems.
Lynch, 1985	A RCT in 30 adults with a LD. Pipothiazine palmitate was given as IM injection for aggressiveness and behaviour that was difficult to manage. There were significant treatment effects over placebo on the CGI and Target Symptom Aggressiveness scales.	This was one of the few studies discovered that was concerned with IM treatment rather than oral, and hence, was excluded on this basis.

Table 1:Studies excluded on full text (continued)

Study	Summary	Reason for exclusion
McConahey, 1971	This was a RCT with a crossover design in 24 female participants with a LD and associated behaviour problems. Chlorpromazine was given to manage the behaviour, however, there was no significant difference between the medication intervention and placebo.	It is unclear whether the medication was administered as IM or orally.
McDougle, 1998	This was a RCT in 31 adults with autism or PDD-not otherwise specified. Risperidone was given to treat various behaviour problems including aggression and SIB. Data was analysed for the sample as a whole but information that could be extracted for those with an IQ<70 showed that 9/11 had some degree of improvement in the treatment group compared to 2/13 in the placebo.	Although most of the participants did have autism as well as a LD (IQ<70), the primary outcome measures were related to autism. Furthermore, data for the participants with a LD could not be extracted separately.
Millichamp, 1987	This was a five-phase double blind, placebo-controlled (non-randomised) study in 6 adults with a LD. Antipsychotic medication was reduced to assess medication effects on a range of stereotypical and collateral behaviours. Medication reduction did not bring about change in any of the behaviours.	There were less than ten participants in the study and this was a medication withdrawal study.
Natrajan, 1997	This was an audit type, case series looking at behavioural problems pre- and post treatment with risperidone in participants with a LD. 13/17 participants showed varying degrees of improvement in 13 areas of behaviour problems.	The age of the participants is not specified in the study.
Saito, 2001	This article looked at the effect of risperidone on the self-mutilation of Lesch-Nyhan syndrome.	The article is in Japanese with no English abstract available. Therefore, it is unknown whether the article meets the inclusion criteria for this review.
Schroeder, 1985	This RCT looked at the effects of neuroleptic medication withdrawal in 23 individuals with a LD. There was inconsistency in the effects observed across individuals in relation to the influence of the withdrawal on behaviour problems.	This was an intervention withdrawal study.
Simon, 1996	This was a case series study of 10 individuals with a LD and mental health problems who were either experiencing significant adverse events or were perceived to be at risk of developing tardive dyskinesia, all in whom conventional antipsychotic medications were substituted with risperidone. All participants were shown to improve in their side effects profiles.	The intervention is used for the management of adverse events and not for a behaviour problem.
Singh, 1993	The effects of two dosages of thioridazine vs. placebo in a double blind, placebo-controlled study were evaluated in 3 children with a LD. A more favourable response towards a higher dose of thioridazine was achieved which appeared to be more effective in reducing stereotypy.	There were less than ten participants in the study.

Table 1:Studies excluded on full text (continued)

Study	Summary	Reason for exclusion
Singh, 1992	This was a randomised, placebo-controlled, double blind trial of zuclopenthixol in 52 inpatients with 'mental handicap' and behaviour problems with or without a psychiatric diagnosis. The results demonstrated a favourable trend for the use of zuclopenthixol among adults with a behaviour problem.	The intervention effectively looked at the continuation of zuclopenthixol versus its withdrawal.
Singh, 1981	This was a RCT including 20 adults and children. Participants were withdrawn from their original dosage of thioridazine and then randomised to either two active medication or placebo conditions. The active medication conditions reduced hyperactivity, and bizarre behaviour.	This was effectively a withdrawal study.
Spivak, 2001	This was an open-label study assessing the efficacy of Zuclopenthixol in the treatment of 15 children and adolescents with a LD and behaviour problems. Zuclopenthixol monotherapy was seen as effective and well tolerated in the treatment of severe behaviour problems in this population, but the authors suggest that double blind, placebo-controlled studies are needed to support their findings.	The age range of the participants is 5-18 years with no separate data for those aged 18. This was not a controlled study and so could not be included for adults and children together.
Tsiouris, 2003	This was a prospective, open trial assessing whether various psychotropic medication treatment of a previously undiagnosed psychiatric disorder would reduce the incidence of SIB. It was suggested that SIB in a 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 medication included in this study. The intervention was the diagnosis of an underlying psychiatric disorder and then the treatment of the identified disorder appropriately.
Vaisanen, 1979		Same as Vaisanen, 1981.
Valdovinas, 2004	This was a double blind, placebo-controlled trial in which risperidone was administered to 21 participants with a LD. The Diagnostic Assessment of the Severely Handicapped (DASH) tool was developed and the effects of risperidone were evaluated using this tool vs. the ABC-Community subscale. The DASH did not appear to be as sensitive a measure of risperidone efficacy as the ABC-Community.	The primary purpose of this study was to assess tool efficacy.
Van Bellinghen, 2001	A RCT of 13 children (IQ range 66-85) in whom persistent behavioural problems persisted. Risperidone treatment proved to be significantly more effective than placebo in behavioural improvement.	The participants had an average IQ of 75.6, which is quite high and unlike the other included studies, it is unknown how many fell within the different levels of a LD.

Table 1:Studies excluded on full text (continued)

Study	Summary	Reason for exclusion
Velarte, 2002	This was a prospective, observational study of risperidone used to manage the behavioural and/or psychotic disorders of 24 participants aged 14-20 with a LD. Risperidone did not produce any adverse events that would warrant discontinuation of treatment and produced improvement in both psychotic and behaviour problems.	The age range of the participants was 14-20 years with no separate data for those aged 18 and over. This was not a controlled study and so could not be included for adults and children together.
White, 1985	The intervention in this RCT was pimozide vs. placebo in 8 participants with a LD who presented with a variety of maladaptive behaviours. Behavioural adjustment was not altered by the medication as was determined by behavioural observations. However, medication induced improvements were shown for irritability and hyperactivity on the ABC dimensions.	There were less than ten participants in the study whom were mainly children.
Williams, 2000	This was an open, case series study exploring the use of atypical antipsychotics in patients with a LD. 9 out of 21 participants were treated with either olanzapine or risperidone for challenging behaviour. Overall, 16 cases were rated as minimally improved or better as was measured by the CGI scale.	There were no separate results for the 9 participants commenced on the antipsychotics for challenging behaviour.

Table 2: Studies included: Adults

Author/ **Evidence category (EC)**	**Medication/ Average daily dose**	**Target behaviour**	**Type of study**	**N**	**Outcome measures**	**Results**
Gagiano 2005 EC I	Risperidone 1.8mg	Various	RCT	Study group: 39, controls: 38	ABC, BPI, CGI-Severity scale, VAS, ESRS	52.8% improved on risperidone compared to 31.3% on placebo.
La Malfa 2001 EC III	Risperidone 2mg ± 1mg	Aggression	Prospective Uncontrolled	18	Handicaps Behaviour and Skills Schedule (HBSs), PIMRA, CGI	Improvement on all 3 scales after 3 months of treatment.
Lott 1996 EC III	Risperidone 5.1mg	Aggression, SIB, property destruction	Prospective Uncontrolled	33	Frequency of target behaviours, global status assessments	61% showed at least 50% reduction in the frequency of 1 or more behaviours. 85% globally improved.
Thalaya-singam 2004 EC III	Clozapine 485mg	Various aggression-related problems	Retrospective Uncontrolled	24	CGI, Overt Aggression Scale (OAS)	29% very much, 42% much and 21% minimally improved. 8% had no change.
Boachie 1997 EC III	Clozapine 640mg in females; 357.1mg in males	Various including aggression, SIB	Retrospective Uncontrolled	17	4-point clinical observation scale	76% rated as improved, 23.5% showed no improvement or became worse.
Wardell 1958 EC I	Chlorpromazine 400-600mg	Various	RCT	Study group: 26, controls: 15	Verbal descriptions of behaviour	No improvement.
Janowsky 2003 EC III	Olanzapine 9.1mg	Various including aggression, SIB	Retrospective Uncontrolled	20	Frequency of behaviours, global behaviour ratings on a 7-point scale	Aggression decreased in 93%, SIB in 86%. Other behaviours decreased in 73%.
La Malfa 2003 EC III	Quetiapine dose range 300-1200mg	Various	Prospective Uncontrolled	15	Handicaps Behaviour and Skills Schedule (HBSs), DOTES	HBSs scores were significantly reduced.

Evidence Categories - I: randomised controlled trial (RCT); II: controlled study without randomisation; III: other non-experimental studies such as case series, SIB: self-injurious behaviour, ABC: Aberrant Behaviour Checklist, BPI: Behaviour Problems Inventory, CGI: Clinical Global Impressions, VAS: Visual Analogue Scale, ESRS: Extrapyramidal Symptom Rating Scale, PIMRA: Psychopathological Instrument for Mentally Retarded Adults, DOTES: Dosage Record Treatment Emergent Symptom scale.

Table 2: Studies included: Adults *(continued)*

Author/ **Evidence category (EC)**	**Medication/ Average daily dose**	**Target behaviour**	**Type of study**	**N**	**Outcome measures**	**Results**
Malt 1995 EC II	Zuclopenthixol – 1st phase: 5.5mg, 2nd phase: 5.13mg vs. Haloperidol – 1st phase: 1.56mg, 2nd phase: 1.23mg	Various including SIB, aggression	Prospective Crossover	34	Handicaps Behaviour and Skills Schedule (HBSs), CGI, UKU side effects scale	Zuclopenthixol was found to be more effective than haloperidol.
Gualtieri 1990 EC III	Fluphenazine 1-15mg	SIB	Prospective Uncontrolled	15 but only 12 eligible	Individual Behaviour Observations (IBO), neuroleptic side effects checklist, Simpson-Angus EPS ratings, AIMS	9/12 (75%) identified as responders on IBO. 3/12 (25%) were found to be responders on a lower dosage.
Elie 1980 EC I	Thioridazine 50mg	Aggression	RCT	51 (unknown how many were in study/ control groups)	TSA, Chief Aggressive Manifestations (CAM), CGI	No improvement. Medication aggravated the participants' conditions.

Evidence Categories - I: randomised controlled trial (RCT); II: controlled study without randomisation; III: other non-experimental studies such as case series, SIB: self-injurious behaviour, CGI: Clinical Global Impressions, UKU: Udvalg for Kliniske Undersøgelser Side Effect Rating Scale, EPS: extra-pyramidal symptoms, AIMS - Abnormal Involuntary Movements Scale, TSA: Target Symptom Aggresivity Scale

Table 3: Studies included: Adults and children

Author/ **Evidence category (EC)**	**Medication/ Average daily dose**	**Target behaviour**	**Type of study**	**N**	**Outcome measures**	**Results**
Zarcone 2001 EC II	Risperidone Low dose: - children 1mg - adults 2mg High dose: - children 1.8mg - adults 3.5mg	SIB, aggression, property destruction, stereotypy	Prospective Crossover between low vs. high dose	20	ABC, NCBR Form (children only), SIB-Q (adults only), CGI, DISCUS, neuroleptic side effects checklist	No significant dose effects on ABC. Better effects with high dose on NCBR Form. Better effects with low dose on SIB-Q. No difference on CGI.
Vanden Borre 1993 EC I	Risperidone 8.3mg	Various including aggression, hostility, hyperactivity	RCT crossover	30	ABC, CGI, VAS, ESRS	Decrease in ABC score for the risperidone group (27.5%) in the second double blind phase. CGI showed improvement in risperidone group.
Aman 1989 EC I	Haloperidol Low dose: 0.025mg/kg High dose: 0.05mg/kg	Stereotypy	RCT crossover	20	ABC, Fairview Problem Behaviour Checklist (FPBC), direct observations	No improvement on ABC/ FPBC. Movement increased with medication (at high dose) and inactivity decreased. High stereotypy participants had better effect, low stereotypy deteriorated.
Vaisanen 1981 EC I	Haloperidol - dose range 10-60mg vs. Thioridazine - dose range 100-600mg	Restlessness, behavioural problems including aggression, SIB	RCT crossover	30	Sheet designed for this study rating 5 behavioural problems, global assessment, ESRS	13 classified as responders to both medications, 8 to haloperidol only and 6 to thioridazine only. 3 were non-responders.
Vaisanen 1975 EC I	Sulpiride - dose range 50-100mg/ t.i.d. vs. Chlorpromazine - dose range 25-50mg	Restlessness, behavioural problems including aggression, SIB	RCT crossover	60	Sheet designed for this study rating 7 behavioural problems, global assessment	More positive behaviour with sulpiride over placebo. No difference between the two medications.

Evidence Categories - I: randomised controlled trial (RCT); II: controlled study without randomisation, SIB: self-injurious behaviour, ABC: Aberrant Behaviour Checklist, NCBR-F: Nisonger Child Behaviour Rating Form, SIB-Q: Self Injurious Behaviour Questionnaire, CGI: Clinical Global Impressions, DISCUS:

Dyskinesia Identification System: Condensed User Scale, VAS: Visual Analogue Scale, ESRS: Extrapyramidal Symptom Rating Scale

Table 3 Studies included: Adults and children *(continued)*

Author/ **Evidence category (EC)**	**Medication/ Average daily dose**	**Target behaviour**	**Type of study**	**N**	**Outcome measures**	**Results**
Weir 1968 EC I	Pericyazine (P) vs. Chlorpromazine (C) - dosages unknown	Participants described as 'disturbed'	RCT	45; P group: 22, C group: 21 (2 withdrawn prior to analysis	A day behaviour rating scale adapted from previous research, night rating scale developed for this study	No improvement with medications over placebo, but differences between P vs. no intervention and C vs. no intervention observed on the day rating scale.

Evidence Categories - I: randomised controlled trial (RCT)

Table 4: Studies included: Children

Author/ **Evidence category (EC)**	**Medication/ Average daily dose**	**Target behaviour**	**Type of study**	**N**	**Outcome measures**	**Results**
Shea 2004 EC I	Risperidone 1.17mg	Various	RCT	Study group: 40; controls: 39	ABC, NCBR-F, VAS, CGI-change, safety measures	64% improved with R compared to 31% with P on ABC ratings. 87% global improvement with R in relation to 40% on P.
Aman 2002 EC I	Risperidone 1.16mg	Various	RCT	Study group: 55; controls: 63	NCBR-Form, ABC, CGI, BPI, VAS, ESRS	Problem behaviours decreased, prosocial increased. 76.9% in R group improved on CGI and 33.4% in P group.
R.U.P.P. Autism Network 2002 EC I	Risperidone dose range 0.5-3.5mg	Various including tantrums, aggression, SIB	RCT	Study group: 49; controls: 52	ABC-Irritability subscale, CGI-Improvement scale, Simpson-Angus Scale, AIMS	56.9% reduction in Irritability score for R group compared to 14.1% in P. Some degree of improvement on CGI for 69% of R group versus 12% in P.
Snyder 2002 EC I	Risperidone 0.98mg	Various including aggression, impulsivity, defiance of authority figures, property destruction	RCT	Study group: 53; controls: 57	Conduct Problem subscale of the NCBR-Form, ABC, CGI, BPI, VAS, ESRS	All outcome measures showed improvement in R group. 20.9% reduction in scores on the NCBR-F subscale for P versus 47.3% on R.
Buitelaar 2001 EC I	Risperidone 2.9mg	Severe aggression	RCT	Study group: 19; controls: 19	CGI-Severity of illness scale, Modified Overt Aggression Scale (OAS-M), ABC, ESRS	Overall improvements were found on all scales for the R group during the trial period. A subsequent washout period resulted in deterioration for this group.

Evidence Categories - I: randomised controlled trial (RCT), ABC: Aberrant Behaviour Checklist, NCBR-F: Nisonger Child Behaviour Rating Form, VAS: Visual Analogue Scale, CGI: Clinical Global Impressions, R: Risperidone, P: Placebo, SIB: self-injurious behaviour, BPI: Behaviour Problems Inventory, ESRS: Extrapyramidal Symptom Rating Scale, AIMS: Abnormal Involuntary Movement Scale

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